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SRI International, Menlo Park, Calif

Prepared for

Environmental Protection Agency, Washington, D C

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A STUDY OF INDUSTRIAL DATA ON CANDIDATE CHEMICALS FOR TESTING

June 1978

Research Request No. 3

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16. ABSTRACT

This report describes the work done on Research Request No. 3 as specified by the Project Officer.

Data were collected for the chemicals in two classes, alkyl phthalates and cresols. The phthalates class included thirty-seven alkyl phthalates believed to be commercially significant at the present time. The cresol class included ortho-cresol, meta-cresol, para-cresol, mixed cresols, and cresylic acid. The following information is provided on the two classes: physical and chemical properties, contaminants; composition of mixtures; production and trade statistics, current (and in some cases, past) uses; names and locations of producers; worker exposure and occupational standards; environmental emissions, mode of entry, transport, and degradation in the environment; and biological effects (including ecological hazards and human health hazards).

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Phthalates	Carcinogens	Chemical Economics	07/03 05/03
Chemical Industry	Mutagens	Cresols/Phthalates	07/03
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A STUDY OF INDUSTRIAL DATA ON CANDIDATE CHEMICALS FOR TESTING

Contract No. 68-01-4109
Research Request No. 3

Project Officer: James Darr

Prepared for

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This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

PREFACE

This report was prepared by an interdisciplinary team under the general guidance of the EPA project officer, James Darr. The SRI team consisted of C. Tucker Helmes, Barbara Lewin, Kirtland McCaleb (Project Leader), Howard Peters, Margaret Power, Caroline Sigman, Patricia Sullivan, Susanne Urso, Janet Walker, and Rose Wright.

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I. INTRODUCTION

A. Background

The Office of Toxic Substances of the Environmental Protection Agency needs to produce information packages as a basis for decisions about testing chemicals for unreasonable risk to human health or the environment. Contract No. 68-01-4109 with SRI International (formerly Stanford Research Institute) was established as a first step in producing these packages. It calls for SRI to provide, in answer to Research Requests provided by the Project Officer, selected economic, chemical, and biological information on selected commercial chemicals.

B. Objectives

The objectives of this study were to provide selected information as designated by the Project Officer concerning physical and chemical properties, occupational and environmental exposure, and biological effects on two classes of chemicals of interest: alkyl phthalates and cresols. The data are presented in tabular summary and text form for each class of chemicals.

II. SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

A. Summary

This report describes the work carried out on Research Request No. 3.

Data were collected on physical and chemical properties, production and trade statistics, past and current uses, occupational exposure and standards, entry, transport, and degradation in the environment, ecological effects and human health hazards for the commercially significant members of the two classes of chemicals.

B. Conclusions and Recommendations

Because Research Request No. 3 was designed to provide certain specified information on selected chemicals, no conclusions were drawn from the studies performed, nor are any recommendations appropriate.

III. STUDIES OF SELECTED CHEMICALS

ALKYL PHTHALATES

A. Summary of Physical and Chemical Data

1. Identification and Properties of Compounds

a. Structure and Nomenclature

This class of chemicals includes diesters of ortho-phthalic acid in which at least one ester group is linked to a nonaromatic carbon. Excluded from this study are the esters of isophthalic acid, terephthalic acid, and tetrahydrophthalic acid, and polymeric phthalates derived from glycols and phthalic acid or anhydride.

The alkyl phthalates included in this study are those believed to be commercially significant at the present time based largely on two publications:

1) The 1976 and 1975 editions of Synthetic Organic Chemicals, U.S. Production and Sales, published by the U.S. International Trade Commission;

2) The 1977 edition of the Directory of Chemical Producers, published by SRI International.

The TSCA Inventory list and the Plasticizers chart in the 1976-1977 edition of the Modern Plastics Encyclopedia were also consulted. However, if the alkyl phthalate was not listed in either Synthetic Organic Chemicals or the Directory of Chemical Producers, it was not considered to be commercially produced at present. The alkyl phthalates meeting the above requirements are listed in Table I together with their molecular structures and physical properties. Molecular structures of the alkyl groups are not specifically drawn in Table I in cases where no systematic name exists for the compound. The alkyl group is represented by its molecular formula (e.g., isodecyl as $-C_{10}H_{21}$) with no indication of location and extent of branches.

The terminology commonly used for the C_6-C_{13} alkyl groups of alkyl phthalates does not follow the strict nomenclature for alkyl groups and, in some cases, indefinite names appear to be used to allow the manufacturer some latitude in the composition of the products sold for their functional properties. In general, the term "iso" is used to denote the mixture of primary alkyl groups formed when olefins are converted to alcohols by reaction with carbon monoxide and hydrogen in the oxo process. For example, diisodecyl phthalate is produced by the reaction of phthalic anhydride with isodecyl alcohol derived from nonene (propylene trimer) by the oxo reaction. To further complicate proper identification, the "iso" part of the name is sometimes dropped (e.g., isotridecyl is more frequently referred to as merely tridecyl).

The names used for the C_8 alkyl groups of alkyl phthalates are particularly confusing since the general term 'octyl' is often used without any differentiation between n-octyl, 2-ethylhexyl, and isooctyl. It appears that 2-ethylhexyl is most frequently the alkyl group intended when the general term octyl is used, however.

Because a number of these alkyl phthalates are specifically mentioned many times in the text of this report, particularly in the environmental and biological sections, we have adopted the following abbreviations.

Key to Abbreviations

BBP	Butyl benzyl phthalate
BPBG	Butyl phthalyl butyl glycolate
DAP	Diallyl phthalate
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DEP	Diethyl phthalate
DIBP	Diisobutyl phthalate
DIDP	Diisodecyl phthalate
DIOP	Diisooctyl phthalate
DMEP	Di(2-methoxyethyl) phthalate
DMP	Dimethyl phthalate
DNP	Dinonyl phthalate
DOP	Dioctyl phthalate
DPP	Dipropyl phthalate
DUP	Diundecyl phthalate
EPEG	Ethyl phthalyl ethyl glycolate
MBP	Monobutyl phthalate

Table I

Physical and Chemical Properties of Some Alkyl Phthalates

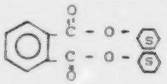
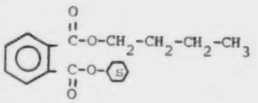
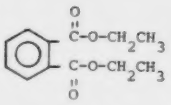
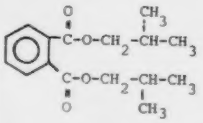
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P [c]
84-61-7	Dicyclohexyl phthalate (1,2-Benzenedicarboxylic acid, dicyclohexyl ester)	 $C_{20}H_{26}O_4$	58-65	212-218 at 5mm 231-248 at 10mm	1.29	Insoluble in water, soluble in alcohol and ether	<0.1 at 150°C	6.94
84-64-0	Butyl cyclohexyl phthalate (1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester)	 $C_{18}H_{24}O_4$		189-222 at 5mm	1.076			6.26
84-66-2	Diethyl phthalate (1,2-Benzenedicarboxylic acid, diethyl ester)	 $C_{12}H_{14}O_4$	-4	296	1.115-1.119	0.1% at 18°C, miscible with alcohol and ether, soluble in acetone and benzene	55 at 200°C	3.42 3.22[e]
84-69-5	Diisobutyl phthalate (1,2-Benzenedicarboxylic acid, bis(2-methylpropyl)ester)	 $C_{16}H_{22}O_4$	-50	327	1.040 (20°C)	<0.025%		5.32

Table I (Continued)

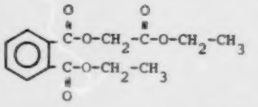
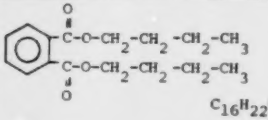
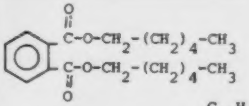
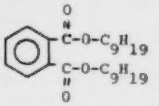
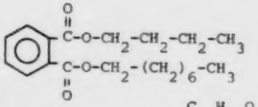
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P[c]
84-72-0	**Ethyl phthalyl ethyl glycolate** (1,2-Benzenedicarboxylic acid, 2-ethoxy-2-oxoethyl ethyl ester)	 $C_{14}H_{16}O_6$	<-35	190 at 5mm	1.177	0.050		2.59
84-74-2	Dibutyl phthalate (1,2-Benzenedicarboxylic acid, dibutyl ester)	 $C_{16}H_{22}O_4$	-40	335	1.042-1.049	0.013%, miscible with alcohol, ether, and benzene	<0.01 at 20°C 1.1 at 150°C 14 at 200°C	5.58 3.70^e
84-75-3 g	Di-n-hexyl phthalate (1,2-Benzenedicarboxylic acid, dihexyl ester)	 $C_{20}H_{30}O_4$	<50 (pour point)	210 at 5mm	0.900-1.007	<0.025%	5 at 210°C	7.74
84-76-4	Dinonyl phthalate[a] (1,2-Benzenedicarboxylic acid, dinonyl ester)	 $C_{26}H_{42}O_4$		413	0.965-0.972	Insoluble in water	1 at 205°C	$10.98^{d,i}$
84-78-6	n-Butyl n-octyl phthalate (1,2-Benzenedicarboxylic acid, butyl octyl ester)	 $C_{20}H_{30}O_4$	<-50	225 at 5mm	0.993			7.74

Table I (Continued)

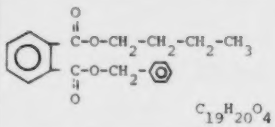
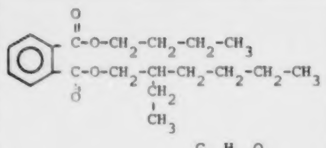
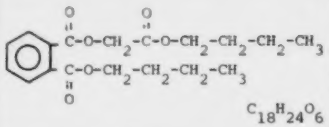
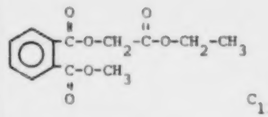
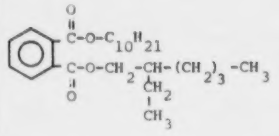
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P[c]
85-68-7	Butyl benzyl phthalate (1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester)	 $C_{19}H_{20}O_4$		370	1.111- 1.123	Insoluble in water	0.16 at 150°C 1.9 at 200°C	5.63
85-69-8	Butyl 2-ethylhexyl phthalate (1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester)	 $C_{20}H_{30}O_4$	-37 (pour point)	224 at 5mm	0.9941		1.8 at 200°C	7.61
85-7[illegible]1	Butyl phthalyl butyl glycolate (1,2-Benzenedicarboxylic acid, 2-butoxy-2-oxoethyl butyl ester)	 $C_{18}H_{24}O_6$		219 at 5mm	1.097	0.018%		4.75
85-71-2	Methyl phthalyl ethyl glycolate (1,2-Benzendicarboxylic acid, 2-ethoxy-2-oxoethyl methyl ester)	 $C_{13}H_{14}O_6$	<-35	189 at 5mm	1.220	0.053%		2.05
89-13-4[g]	2-Ethylhexyl isodecyl phthalate[a] (Phthalic acid, 2-ethylhexyl 8-methylnonyl ester)	 $C_{26}H_{42}O_4$	-48 (pour point)	245 at 5mm	0.973		0.54 at 200°C	10.72[d,f]

Table I (Continued)

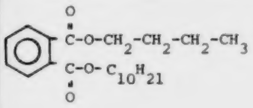
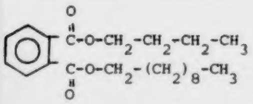
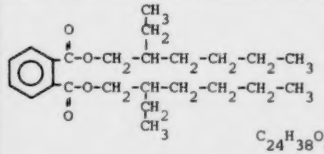
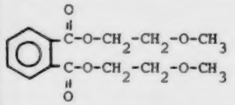
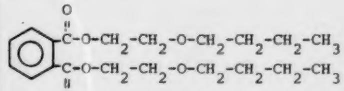
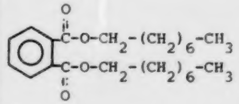
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P[c]
89-18-9[g]	Butyl isodecyl phthalate[a] (1,2-Benzenedicarboxylic acid, butyl 8-methylnonyl ester)	 $C_{22}H_{34}O_4$	-50	229 at 5mm	0.991-0.998			8.69[f]
89-19-0	n-Butyl n-decyl phthalate (Phthalic acid, butyl decyl ester)	 $C_{22}H_{34}O_4$	-50	220 at 5mm	0.991			8.62
117-81-7	Bis(2-ethylhexyl) phthalate (1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester)	 $C_{24}H_{38}O_4$	-46 (pour point)	231 at 5mm 236 at 10mm	0.980-0.9861	<0.01% at 20°	1.20-1.32 at 200°C	9.64
117-82-8	Bis(2-methoxyethyl) phthalate (1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl)ester)	 $C_{14}H_{18}O_6$	-40	190-210 at 340mm	1.171 (20°C)	0.838%	<0.01 at 20°C 0.25 at 150°C	1.10
117-83-9	Bis(2-butoxyethyl) phthalate (1,2-Benzenedicarboxylic acid, bis(2-butoxyethyl)ester)	 $C_{20}H_{30}O_6$		210-233 at 4mm	1.063	<0.1% at 25°C	<0.01 at 20°C 0.06 at 150°C	4.34
117-84-0	Di-n-octyl phthalate (1,2-Benzenedicarboxylic acid, dioctyl ester)	 $C_{24}H_{38}O_4$	-25	220-248 at 4mm	0.978 (20°C)	Insoluble in water	<0.20 at 150°C	9.90

Table I (Continued)

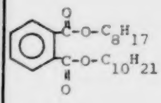
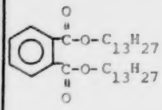
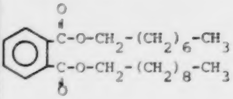
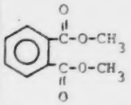
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P[c]
119-05-1[g]	Isooctyl isodecyl phthalate[a] (Phthalic acid, 6-methylheptyl 8-methylnonyl ester)	 $C_{26}H_{42}O_4$	-48	235-248 at 4mm	0.967			10.72[d,f]
119-06-2	Bis(tridecyl) phthalate[a] (1,2-Benzenedicarboxylic acid, ditridecyl ester)	 $C_{34}H_{58}O_4$	-37 (pour point)	240 at 2mm	0.9512			15.30[d,f]
119-07-3[g]	n-Decyl n-octyl phthalate (1,2-Benzenedicarboxylic acid, decyl octyl ester)	 $C_{26}H_{42}O_4$	-28	250 at 5mm	0.970			10.98[d]
131-11-3	Dimethyl phthalate (1,2-Benzenedicarboxylic acid, dimethyl ester)	 $C_{10}H_{10}O_4$	0	283	1.194 (20°C)	0.4%, miscible with alcohol and ether, soluble in benzene	<0.01	2.34 2.22[e]

Table I (Continued)

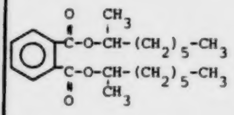
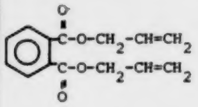
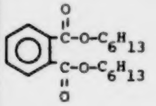
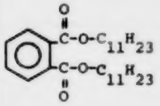
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P[c]
131-15-7	Di-sec-octyl phthalate (1,2-Benzenedicarboxylic acid, bis(1-methylheptyl)ester) (also known as dicapryl phthalate)	 $C_{24}H_{38}O_4$	<-60	215-240 at 4mm	0.965-0.978	<0.03%		9.46
131-17-9	Diallyl phthalate (1,2-Benzenedicarboxylic acid, di-2-propenyl ester)	 $C_{14}H_{14}O_4$	65	290	1.120 (20°C)	0.01%		2.72
146-50-9	Diisohexyl phthalate [a] (Phthalic acid, diisohexyl ester)	 $C_{20}H_{30}O_4$						7.48[f]
3648-20-2	Diundecyl phthalate[a] (1,2-Benzenedicarboxylic acid, diundecyl ester	 $C_{30}H_{50}O_4$	-20		0.95			13.14[d,f]

Table I (Continued)

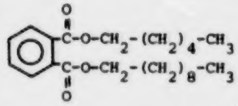
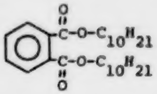
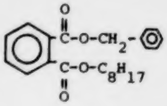
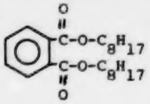
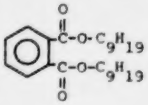
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P[c]
25724-58-7[g]	n-Decyl n-hexyl phthalate (Phthalic acid, decyl hexyl ester)	 $C_{24}H_{38}O_4$						9.90
26761-40-0	Diisodecyl phthalate[a] (1,2-Benzenedicarboxylic acid, diisodecyl ester)	 $C_{28}H_{46}O_4$	-37	356	0.961- 0.967		0.3 at 200°C	11.80[d,f]
27215-22-1	Isooctyl benzyl phthalate[a] (Phthalic acid, benzyl isooctyl ester)	 $C_{23}H_{28}O_4$			1.069		0.5 at 200°C	7.67[f]
27554-26-3	Diisooctyl phthalate[a] (1,2-Benzenedicarboxylic acid, diisooctyl ester)	 $C_{24}H_{38}O_4$	-46 (pour point)	228-229 at 5mm	0.986 (20°C)	Insoluble in water	1.0 at 200°C	9.64[f]
28553-12-0	Diisononyl phthalate[a] (1,2-Benzenedicarboxylic acid, diisononyl ester	 $C_{26}H_{42}O_4$	<-50.0	222-230 at 5mm	0.982		<0.01	10.50[d,f]

Table I (Continued)

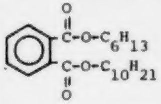
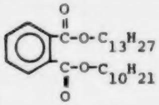
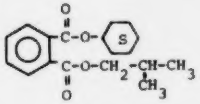
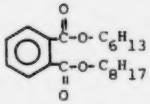
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula[a]	Melting Point °C	Boiling Point °C	Specific Gravity 25°C	Solubility[b]	Vapor Pressure mm Hg	Partition Coefficient Log P [c]
61702-81-6	Hexyl isodecyl phthalate[a] (1,2-Benzenedicarboxylic acid, hexyl isodecyl ester)	 $C_{24}H_{38}O_4$						9.77[f]
61886-60-0	Isodecyl tridecyl phthalate [a]	 $C_{31}H_{52}O_4$			0.955			13.55[d,f]
-	Cyclohexyl isobutyl phthalate	 $C_{18}H_{24}O_4$						6.13
-	Hexyl isooctyl phthalate[a]	 $C_{22}H_{34}O_4$						8.69[f]

Table I (Concluded)

Source: Compiled from several sources, including Autian (1973), Buttrey (1960), Modern Plastics Encyclopedia (1976), and Weast (1977).

a. See discussion in text concerning structure of groups with non-systematic names.

b. Solubilities are for water unless otherwise noted.

c. Partition coefficient is expressed as log P, defined as the $\log\left[\frac{\text{concentration in octanol}}{\text{concentration in water}}\right]$ at equilibrium calculated according to the method suggested by Leo, A., Jow, P.Y.C., Silipo, C., & Hansch, C. (1975), J. Med. Chem., 18(9), 865-868.

d. Calculated values for log P's greater than 10 may be artifactual and may not reflect values which would be obtained experimentally.

e. Measured using toluene as the organic phase; cited in Tomita, A., Ebina, N., & Tamai, Y. (1977), J. Amer. Chem. Soc., 99, 5725.

f. Calculation of log P requires that the structure be known. For any alkyl group in this table not having a systematic name, the following assumptions regarding its structure were made (for log P calculations only):

1) Linearity was assumed in the absence of any qualifier such as iso;
2) When the prefix iso was present, it was taken in its strict sense: one methyl group on the next-to-last carbon atom and no other branches;
3) Ethylhexyl was assumed to be 2-ethylhexyl

g. To reflect common usage, the name listed here for this compound is slightly different (more specific in some cases, less specific in others) than the Chemical Abstracts Services index name, which is shown in parenthesis.

b. Chemical and Physical Properties

(1) Chemical Properties

Alkyl phthalates undergo the typical reactions of carboxylic esters, e.g., saponification by strong bases, hydrolysis in the presence of strong aqueous acids, reduction to alcohols by the action of hydrogen, ester interchange, and conversion to amides by reaction with ammonia (Morrison & Boyd, 1973).

Phthalate plasticizers can undergo oxidation during plastics processing, forming peroxides which later decompose with development of colored and odorous compounds. Antioxidants such as bisphenol A are added to the resin to inhibit this reaction (Fishbein & Albro, 1972).

(2) Physical Properties

Selected physical properties of the alkyl phthalates, where available, are listed in Table I.

2. Known or Likely Contaminants

Since alkyl phthalates are used almost exclusively as plasticizers and the purity requirements for this use are very high, most products are offered in purities of 99% or greater, with a residual maximum acidity of 0.01% (presumably monoalkyl phthalates containing one carboxylic acid group). Phthalic anhydride, from which the alkyl phthalates are prepared, is usually 99.5% pure. The remaining 0.5% could be isophthalic acid, terephthalic acid, and maleic anhydride; these compounds would be converted to the corresponding diesters in the esterification process.

3. Composition of Mixtures

As indicated in Section III A.1.a. above, many of these products are really isomeric mixtures because they are prepared by esterifying phthalic anhydride with an isomeric mixture of alcohols derived from the oxo reaction on olefins - a reaction which results in alcohols with varying amounts of branching. Hence, the resulting products, although identified by a single name are not pure compounds. In addition, some producers offer an ester made from a mixture of two or more alcohols. Thus, di-(heptyl, nonyl) phthalate may consist of diheptyl phthalate, dinonyl phthalate and heptyl nonyl phthalate. An even more complicated mixture may be present in a product designated as di(heptyl, nonyl, undecyl) phthalate.

B. Summary of Data on Occupational and Environmental Exposure

1. Names and Locations of Producers

The thirty-seven alkyl phthalates believed to be commercially produced at the present time are listed in Table II along with the twenty-seven companies that produce them. These companies and locations of their producing plants are listed in Table III. The numbers in the columns in Table II refer to the sources used to determine the commerciality of the chemicals (see footnote to Table II). The 1976 edition of Synthetic Organic Chemicals was given first priority since the minimum quantity which the International Trade Commission requires for inclusion therein is 5,000 pounds (or $5,000 worth) per producer. The requirements for the 1975 Synthetic Organic Chemicals and the 1977 Directory of Chemical Producers are 1,000 pounds (or $1,000 worth) per producer.

2. Production and Trade Statistics

U.S. production of alkyl phthalates was reported to the International Trade Commission as early as 1921. Table IV summarizes U.S. production of some alkyl phthalates since 1970. Tables V and VI summarize data for U.S. imports and exports since 1970. For those alkyl phthalates not found in Table IV, the minimum production level can be estimated by consulting Table II. For those chemicals in the 1976 Synthetic Organic Chemicals (denoted by a 6), each producer made at least 5,000 pounds (or $5,000 worth). For those chemicals not in the 1976 Synthetic Organic Chemicals, but in the 1975 edition (denoted by a 5) or in the 1977 Directory of Chemical Producers (denoted by a 7), each producer made at least 1,000 pounds (or $1,000 worth). For example, at least 10,000 pounds of dicyclohexyl phthalate (two producers) were produced in 1976, at least 2,000 pounds of dinonyl phthalate (two producers) were produced in 1975, and at least 1,000 pounds of hexyl isodecyl phthalate (one producer) were produced in 1977. In the case of di-n-hexyl phthalate, at least 10,000 pounds (two producers) were produced in 1976. Since the

Table II

Producers of Some Alkyl Phthalates [a,b]

Phthalate ester	Akzona	BASF Wyandotte	Chemicals & Pollution Sciences	Continental Oil	Eastman Kodak	Exxon[g]	FMC Corp.	B.F. Goodrich	W.R. Grace[e]	C.P. Hall	Hardwicke Chemical Co.	Int'l Minerals & Chemicals	Interstab Chemicals	Kay-Fries Chemicals	Monsanto[c,g]	Occidental	Pfizer	Reichhold	Richardson-Merrell	Sherwin-Williams	Stauffer	Sybron	Teknor Apex	Tenneco[g]	Union Camp	Union Carbide Corp.	U.S. Steel
Butyl benzyl															6 (N.J.)												
Butyl cyclohexyl			6																								
n-Butyl n-decyl																		7									
Butyl 2-ethylhexyl									7						5												
Butyl isodecyl									7																		
n-Butyl n-octyl					7													6									6
Butyl phthalyl butyl glycolate[f]															6 (Mo.)												
Cyclohexyl isobutyl															5 (Mass.)												
n-Decyl n-hexyl*		6		6					6														6	6			
n-Decyl n-octyl																		6					6				6
Diallyl							6				7																
Di(2-butoxyethyl)	5									6																	
Dibutyl*		6			6				6	7		5			6		7	6	7	6					6	6	6
Dicyclohexyl															6 (Mass.)		6										
Diethyl*					6									6	6 (Mo.)		6										
Di(2-ethylhexyl)*		6		6	6	6		6	6						6 (Tx.)		7	6					6	6		5	6
Di-n-hexyl													7				6						7				6
Diisobutyl									7						7 (Mo.)												
Diisodecyl		6		6	5	6		7	6						6	6	7	6					6	6			6
Diisohexyl						5																					
Diisononyl						6																					

Table II (Concluded)

	Akzona	BASF Wyandotte	Chemicals & Pollution Sciences	Continental Oil	Eastman Kodak	Exxon^g	FMC Corp.	B.F. Goodrich	W.R. Grace^e	C.P. Hall	Hardwicke Chemical Co.	Int'l Minerals & Chemicals	Interstab Chemicals	Kay-Fries Chemicals	Monsanto^{c,g}	Occidental	Pfizer	Reichhold	Richardson-Merrell	Sherwin-Williams	Stauffer	Sybron	Teknor Apex	Tenneco^g	Union Camp	Union Carbide Corp.	U.S. Steel
Diisooctyl																	7^d	6^d					7^d				6^d
Di(2-methoxyethyl)					6																7						
Dimethyl*					6									6	6 (Mo.)		6	6				6					
Dinonyl																	5	5									
Di-n-octyl					5																						
Di-sec-octyl																									6		
Ditridecyl*						6			6							6	7	6					6	6			6
Diundecyl															5 (Tx.)								5				
2-Ethylhexyl isodecyl																							7				
Ethyl phthalyl ethyl glycolate^f															5 (Mo.)												
Hexyl isodecyl																	7										
Hexyl isooctyl																	6										
Isodecyl tridecyl																							7				
Isooctyl benzyl															7 (NJ)												
Isooctyl isodecyl																	7	7					7				
Methyl phthalyl ethyl glycolate^f															7 (Mo.)												

* Current production volumes given in Table IV.

a. Numbers in columns refer to the following sources:
   6= 1976 Synthetic Organic Chemicals, U.S. Production and Sales
   5= 1975 Synthetic Organic Chemicals, U.S. Production and Sales
   7= 1977 Directory of Chemical Producers
   See discussion in text for priority of these sources.

b. See Table III for locations of producers.

c. State in parentheses refers to specific Monsanto location, where known.

d. This company also makes "diisooctyl and mixed dioctyl phthalates."

e. This company is listed in the 1976 Synthetic Organic Chemicals as producing "dicyclohexyl 2-ethylhexyl phthalate," which appears to be a typographical error.

f. Hercules Inc. is listed in the 1976 Synthetic Organic Chemicals as a producer of "all other glycol phthalate esters."

g. This company is listed in the 1976 Synthetic Organic Chemicals as a producer of "all other phthalic anhydride esters."

Table III

Alkyl Phthalate Producers and Locations

Company	Division	Location
Akzona Inc.	Armak Co., subsidiary Armak Industrial Chemicals Division	Philadelphia, Pa. 19135
BASF Wyandotte Corp.	Colors & Intermediates Group	Kearny, N.J. 07032
Chemical & Pollution Sciences, Inc.	CPS Chemical Company Division	Old Bridge, N.J. 08857
Continental Oil Co.	Conoco Chemicals Division	Aberdeen, Miss. 39730
Eastman Kodak Co.[a]	Eastman Chemical Products, Inc., subsidiary Tennessee Eastman Co.	Kingsport, Tenn. 37662
Exxon Corp.	Exxon Chemical Co., division Exxon Chemical Company, U.S.A.	Baton Rouge, La. 70821
FMC Corp.	Chemical Group Industrial Chemical Division	Baltimore, Md. 21226
B. F. Goodrich Co.	B. F. Goodrich Chemical Co., division	Avon Lake, Ohio 44012
W. R. Grace & Co.	Hatco Group Hatco Chemical Division	Fords, N.J. 08863
C. P. Hall Co.		Chicago, Ill. 60638
Hardwicke Chemical Co.		Elgin, S.C. 29045
International Minerals & Chemical Corp.	IMC Chemical Group, Inc., subsidiary	Terre Haute, Ind. 47808
Interstab Chemicals Inc.		New Brunswick, N.J. 08903
Kay-Fries Chemicals Inc.		Stony Point, N.Y. 10980
Monsanto Co.	Monsanto Chemical Intermediates Co. Monsanto Industrial Chemicals Co.	St. Louis, Mo. 63177 Bridgeport, N.J. 08014 Everett, Mass. 02149 Texas City, Tex. 77590
Occidental Petroleum Corp.	Hooker Chemical Corp., subsidiary RUCO, subsidiary	Hicksville, N.Y. 11802

Table III (Continued)

Pfizer Inc.	Chemicals Division	Greensboro, N.C. 27403
Reichhold Chemicals, Inc.		Carteret, N.J. 07008
Richardson-Merrell Inc.	J. T. Baker Chemical Co., subsidiary	Phillipsburg, N.J. 08865
Sherwin-Williams Co.	Chemicals Group Chemicals Division	Chicago, Ill. 60628
Stauffer Chemical Co.	Specialty Chemical Division	Gallipolis Ferry, W.Va. 25515
Sybron Corp.	The Tanatex Chemical Company, division	Lyndhurst, N.J. 07071
Teknor Apex Co.		Hebronville, Mass. 02703
Tenneco Inc.	Tenneco Chemicals, Inc.	Chestertown, Md. 21620
Union Camp Corp.	Chemical Products Division	Dover, Ohio 44622
Union Carbide Corp.		New York, N.Y. 10017 (Plant location unknown)
United States Steel Corp.	USS Chemicals, division	Neville Island, Pa. 15225

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[a] The location at which this company produces di-n-octyl phthalate is not known.

Table IV

U.S. Production of Alkyl Phthalates
(millions of pounds)

	Phthalic Acid Ester						
	Butyl octyl[a]	Dibutyl	Dicyclohexyl	Diethyl	Di(2-ethylhexyl)	Diisodecyl	Diisooctyl
1970	11.9	22.9	4.5	20.6	350.4	123.4	85.1
1971	16.0	23.0		16.9	386.3	135.7	51.0
1972	11.4	29.1		19.0	435.0	153.3	32.3
1973	7.4	37.9		19.5	378.1	170.8	43.2
1974		35.5		19.7	389.7	146.7	
1975		12.3		11.7	302.5	105.7	
1976		13.7		16.1	296.7	143.1	

	Phthalic Acid Ester						
	Dimethyl	Other dioctyl	Ditridecyl	n-Hexyl n-decyl	n-Octyl n-decyl	Other	Total[b]
1970	8.1		15.1	9.3	58.9	144.7	855.1
1971	10.6		20.3		134.3	172.4	978.2
1972	9.7			16.0		439.9	1145.7
1973	11.3	8.2	19.7			507.1	1203.1
1974	10.0	5.5	27.2	10.2		563.1	1207.3
1975	6.8	10.0	15.7	14.5		424.8	903.8
1976	8.8	17.2	10.5	19.8		516.9	1042.9

Source: Synthetic Organic Chemicals, U.S. Production and Sales, published by the U.S. International Trade Commission.

[a] Includes butyl 2-ethylhexyl phthalate, isobutyl 2-ethylhexyl phthalate, and butyl n-octyl phthalate.

[b] Totals may not add up due to rounding

Table V

U.S. Imports of Alkyl Phthalates[a]
(thousands of pounds)

	Phthalic Acid Ester						
	Butyl benzyl	Diallyl	Dibutyl	Dicyclohexyl	Diethyl	Di(2-ethylhexyl)	Dihexyl
1970				220.3			
1971				250.6			
1972				252.0			
1973		33.1		36.0		78.5	
1974	1,455.9		444.6	252.0		4,179.7	25.9
1975		173.1	179.7	172.5	38.4		
1976		991.7	204.6	240.6	161.0		

	Phthalic Acid Ester						
	Diisodecyl	Diisononyl	Diisooctyl	Dimethyl	Di-n-octyl	Ditridecyl	Diundecyl
1970							
1971							
1972							
1973							
1974	72.3		639.2	45.6	34.4	377.3	1.9
1975	179.9			2.2	220.5		
1976		3,303.9					

Source: Imports of Benzenoid Chemicals and Products, published by U.S. International Trade Commission.

[a] Through principal U.S. customs districts.

Table VI

U.S. Exports of Alkyl Phthalates
(millions of pounds)

	Dioctyl phthalate[a]	Other phthalic acid esters[b]
1970	36.0	36.4
1971	14.6	47.6
1972	16.8	105.8
1973	14.6	78.4
1974	24.7	81.9
1975	20.4	50.9
1976	29.9	75.5

Source: U.S. Exports, FT410, published by the U.S. Department of Commerce, Bureau of the Census.

[a] Dioctyl esters include di(2-ethylhexyl), di(n-octyl), dicapryl, and diisooctyl phthalates, Flexol Plasticizer DOP, and Good-Rite Plasticizer GP-261 (dioctyl phthalate).

[b] Other phthalates include butyl benzyl, di(2-ethylbutyl), di(2-methoxyethyl), diisobutyl, dibutyl, dicyclohexyl, diethyl, diisoamyl, diisodecyl, dimethyl, diphenyl, isoamyl, methyl, and n-octyl n-decyl phthalates, dimethyl glycol phthalate, dimethyl isophthalate, ethyl phthalyl ethyl glycolate, glycol phthalate, di(2-ethylhexyl) hexahydrophthalate and Santicizer 602.

1977 edition of the Synthetic Organic Chemicals is not yet available, it can be assumed that at least 2,000 pounds of di-n-hexyl phthalate (two producers) were produced in 1977.

3. Use Patterns

The alkyl phthalates have largely been used as plasticizers for plastic materials, mostly in polyvinyl chloride resins. Of the estimated 1,078 million pounds of phthalates consumed in the U.S. in 1974, 965 million pounds (89.5%) were used in polyvinyl chloride resins, 35 million pounds (3.2%) in other vinyl resins (e.g., polyvinyl acetate), 30 million pounds (2.8%) in cellulose ester plastics (e.g., cellulose acetate), 22 million pounds (2%) in synthetic elastomers (e.g., chlorinated rubber), 6 million pounds (0.6%) in other polymers (e.g., acrylics), and 20 million pounds (1.9%) in nonplasticizer uses. Nonplasticizer applications include use as carriers or dispersing media for catalysts, pesticides, cosmetics, and colorants, as defoaming agents in paper manufacture, in lubricating oils and munitions, and as a crosslinking agent in unsaturated polyester resins.

Current data on amounts of phthalates used in specific products are not available. However, an estimate has been published of the consumption pattern by application areas for the 822 million pounds of phthalate esters consumed in the U.S. in 1970. This consumption pattern is reproduced in Table VII.

Plasticizers are used at high levels in polyvinyl chloride resins primarily to impart flexibility or a soft feel to the finished product. The proportion of phthalate plasticizer used in polyvinyl chloride resin is usually 55 parts by weight plasticizer to 100 parts by weight resin.

The choice of plasticizers depends on a number of factors: (1) the compatibility of the plasticizer with the resin; (2) the vapor pressure of the plasticizer (it must be low enough to assure retention in the resin during processing); (3) the odor and color of the plasticizer (low odor and color level are needed for consumer products); (4) the relative toxicity of the plasticizer; (5) the resistance of the plasticizer to extraction by solvents, oils, and soapy water; (6) the amount of surface

Table VII

Plasticizer Uses of Phthalate Esters

		Millions of Pounds
Building and Construction		
Wire and cable		185
Flooring		150
Swimming pool liners		20
Weatherstripping		13
Window splines		10
Other		9
	Total	387
Home Furnishings		
Furniture upholstery		90
Wall coverings		38
Housewares		30
Garden hose		15
Appliances		10
Other		20
	Total	203
Transportation		
Upholstery and seatcovers		80
Auto mats		15
Auto tops		12
Other		10
	Total	114
Apparel		
Footwear		45
Outerwear		20
Baby pants		7
	Total	72
Food Surfaces and Medical Products		
Food wrap film		18
Closures		7
Medical tubing		15
Intravenous bags		6
	Total	46
TOTAL		822

Source: Graham (1973)

migration of the plasticizer to adjoining resins; (7) the electrical properties and flammability resistance of the plasticized products (the importance depends on the product's end use); and (8) the cost per pound of the plasticizer (Anon., 1977).

Di(2-ethylhexyl) phthalate (DEHP) is the phthalate ester produced in the largest quantity. It is used as a plasticizer for polyvinyl chloride resins and synthetic rubbers for use in wire insulation, cloth coatings, elastomeric molded materials, and extruded or calendered compositions. Polyvinyl chloride films plasticized with DEHP are used in food packaging, such as wrap for meat and produce packaging, and wheat sealing applications, and in biomedical applications such as blood bags.

Phthalates based on linear C_6-C_{11} alcohols are used heavily as plasticizers in polyvinyl chloride resins for automotive applications, and to a lesser extent, in plastisols and dispersion coatings, and in other film, sheeting, coated fabric, and extrusion applications.

Diisodecyl phthalate is used as a plasticizer in automotive upholstery, polyvinyl chloride and urethane foams, and in wire and cable insulation in combination with diisononyl, ditridecyl, diisooctyl, and di(2-ethylhexyl) phthalates.

Butyl benzyl phthalate (BBP)is primarily used as a plasticizer in polyvinyl chloride flooring but also finds use in polyvinyl chloride foams, coatings, polyvinyl acetate adhesives, and acrylic caulking compounds.

Dibutyl phthalate (DBP) is used mostly as a plasticizer in polyvinyl acetate emulsions for surface coatings, adhesives, paper treating, and textile treating.

Dihexyl phthalate, and to a lesser extent, DBP are used as plasticizers in plastisols for carpet backcoating.

Diethyl and dimethyl phthalate are used almost entirely as plasticizers for cellulose ester plastic film and sheet (photographic, blister packaging, and tape applications) and molded and extruded articles (consumer articles such as toothbrushes, automotive components, tool handles, and toys).

Dicyclohexyl phthalate is a specialty plasticizer used in nitrocellulose lacquers and adhesives.

Diallyl phthalate is used chiefly as a cross-linking agent in unsaturated polyester resins. It is also used to make molded articles (particularly for the electronics industry) and to make insulating varnishes.

4. Occupational Standards and Workers Exposed

Only three of the alkyl phthalates have OSHA regulations governing worker exposure to them: (1) DBP; (2) DEHP; and (3) DMP. These regulations require that an employee's exposure to any one of these phthalates shall not exceed an 8-hour time-weighted average of 5 mg/m^3 in any 8-hour workshift of a 40-hour work week. Although OSHA has not as yet adopted it, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a TLV (threshold limit value) of 5 mg/m^3 for DEP.

Based on the 1974 National Occupational Hazard Survey (NOHS) of plants in selected industries, NIOSH has estimated the total number of workers exposed to certain chemicals in these industries. The estimates of the number exposed to some alkyl phthalates are summarized in Table VIII.

5. Mode of Entry into the Environment

The means by which alkyl phthalates enter the environment are not well defined or understood. One author (Peakall, 1975) has reviewed the available information and has discussed various possibilities:

a. Biosynthesis-- There is some evidence that phthalic acid and alkyl phthalates occur naturally in plants and animals, including microorganisms. Some of the phthalates may have been present as a result of contamination but phthalates were found in some samples even after extreme care was taken to avoid contamination.

b. Loss during manufacturing and processing-- Phthalates could be present in air emissions, aqueous effluents, or solid waste products from phthalate ester manufacturing plants or plastics processing plants.

c. Escape during use of phthalate-containing products-- The uses of phthalates, both as plasticizers (as shown in Table VII) and in nonplasticizer applications can be divided into four broad categories:

Table VIII

Estimated Number of Workers Exposed to Some Alkyl Phthalates In Selected Industries (Based on NOHS)

Phthalate ester	Estimated number of workers
Bis(diethylene glycol monoethyl ether)	7,740
Bis(2-ethylhexyl)	602,250
Bis(tridecyl)	11,250
Butyl benzyl	31,800
Butyl octyl	59,160
Decyl octyl	23,580
Diallyl	19,440
Dibutyl	869,130
Dicapryl (di-sec-octyl)	8,130
Dicyclohexyl	24,600
Didecyl	7,350
Diethyl	1,240,071[a]
Diheptyl	7,620
Dihexyl	9,450
Diisobutyl	8,220
Diisodecyl	80,250
Diisononyl	8,190
Diisooctyl	9,750
Dimethyl	36,480
Dinonyl	7,350
Diundecyl	11,490

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[a] This estimate is considered highly suspect since the quantity of diethyl phthalate produced in 1974 was only 19.7 million pounds -- 1974 production of bis(2-ethylhexyl) phthalate was 389.7 million pounds.

(1) High likelihood of escape. This includes those uses, such as a pesticide carrier, in cosmetics, munitions, and lubricating oils, where the phthalate is not encased in a plastic matrix.

(2) Directly in contact with liquids. This includes uses such as swimming pool liners, garden hoses, and medical products such as blood bags, transfusion and infusion assemblies, artificial kidney connecting tubing, catheters, and many others.

(3) Films or sheets in contact with air. These uses are flooring, weather stripping and window splines, furniture upholstery, auto upholstery and seat covers, wall coverings, auto mats and tops, clothing, and food wrap film.

(4) Materials with low surface contact. This includes cable and wire, housewares, appliances, and miscellaneous uses in building and construction, home furnishings, and transportation.

d. Loss from phthalate-containing plastics in disposal sites-- Although the useful life of plastics varies considerably, most will be discarded within a few years. These materials end up as solid waste and are either incinerated or landfilled. Although most discarded plastics end up in dumps, a small proportion is also distributed throughout the environment, i.e., the plastic cup in the ditch, and the plastic items found floating in the open ocean.

6. Quantities Released into the Environment

The amounts of alkyl phthalates that may enter the environment are not known. However, the author mentioned above (Peakall, 1975) has made some estimates which are summarized here:

a. Biosynthesis-- No attempt was made to estimate this possible source.

b. Loss during manufacturing and processing-- These losses were not estimated, but the comment was made that with a production volume of a billion pounds a year, even a loss factor of 0.1% results in a potential one million pounds of phthalates lost.

c. Escape during use of phthalate-containing products-- Using the above estimates and some arbitrary loss factors, the author made estimates of losses from the use categories described above:

(1) High likelihood of escape. Essentially all of the phthalates in these nonplasticizer uses are believed to enter the environment. The total was estimated at 50 million pounds in 1972.

(2) Directly in contact with liquids. Using an arbitrary loss factor of 1% per year, the loss to the environment from these uses was estimated to have been 570,000 pounds in 1970.

(3) Films or sheets in contact with air. Using an arbitrary loss factor of 0.1% per year, the loss to the environment from these uses was estimated to have been 490,000 pounds in 1970.

(4) Materials with low surface contact. Using an arbitrary loss factor of 0.01% per year, the loss to the environment from these uses was estimated to have been 30 thousand pounds in 1970.

(Note that the total estimated losses of approximately 1 million pounds for these last three (plasticizer) uses is small compared to the estimated 50 million pounds from nonplasticizer uses.)

d. Loss from phthalate-containing plastics in disposal sites-- Of the plastics containing phthalates that end up as solid waste, an estimated 10 to 20 percent are destroyed by high-temperature incineration, and two percent are subjected to open burning or low-temperature incineration. The author assumed that one-third (0.67 percent of total usage) of the phthalates contained in these plastics subjected to open burning or low-temperature incineration would escape destruction and be vaporized.

Because the useful life of most plastics is relatively short (a few years), the rate of discard was considered equal to the rate of consumption. Based on the 1970 consumption estimate of 822 million pounds of phthalate plasticizers and applying the percentage figures estimated by this author, an estimated 82-164 million pounds of phthalates would have been destroyed by high-temperature incineration, 11 million pounds of phthalates would have been destroyed by open burning or low-temperature incineration, and 6 million pounds of phthalates would have been vaporized by open burning or low-temperature incineration. The remaining phthalates would have been contained in landfilled plastic products. An estimate of the amount of phthalates that escape through leaching or vaporization from landfilled plastics was not found in the literature. Excluding this unknown, the author (Peakall, 1975) estimated the environmental input resulting from the manufacture and use of phthalates in plastics at about 8 million pounds per year based on 1970 use estimates.

7. Environmental Transport

Alkyl phthalates occur ubiquitously in the environment, having been identified in a myriad of materials such as water, soil, sediment, air, human and animal tissues and blood, fish, food, solvents and non-phthalate-plasticized plastic products (Marx, 1972; Mathur, 1974a). They have also been reported as possible natural products in animals, plants, microorganisms, and geochemical materials, although the possibility of phthalic acid ester contamination of these materials before or during sampling cannot be excluded (Mathur, 1974a).

Phthalates are believed to be transported in aquatic systems, volatilized at high temperatures and transported through the atmosphere, and to accumulate in aquatic organisms, on sediments and in plants.

Although the phthalate esters are almost insoluble in water and have high boiling points, they appear to migrate readily from plastics and related material into ambient air and liquid or solid media (Mathur, 1974a). Incineration has been reported to be an incomplete method of disposal, as DBP, DEHP, and BPBG were detected in air samples near a municipal incineration plant (Thomas, 1973; Mathur, 1974a).

Several studies have indicated that increased surface area and high temperatures cause volatilization of the normally poorly volatile phthalates from products such as polyvinyl chloride car upholstery and other polyvinyl chloride products (Marx, 1972; Graham, 1973; Mathur, 1974a). Other indications of the atmospheric transport of phthalates have also been reported (Morita, 1974; Giam, et al., 1976). Leaching of phthalates from polymer tubing by water passing through the tubing has been reported, and the amount of phthalates leached has been found to increase with the flow rate (Junk, et al., 1974).

In his review of the literature, Autian (1973) reported that phthalate esters are readily sequestered or absorbed by organic residues and solid surfaces in aquatic systems. Ogner and Schnitzer (1970) and Matsuda and Schnitzer (1971) have investigated the "complexation" of phthalates with fulvic acid, a water-soluble humic material which occurs widely in soils and waters. They suggested that the fulvic acid can form stable complexes with the phthalate esters, thus solubilizing them and possibly mediating their transport in an aquatic environment. Under laboratory conditions, Matsuda and Schnitzer (1971) found that the amount of phthalate solubilized by the fulvic acid was dependent on the structure of the specific ester, with DEHP complexed the most and DBP the least. Increasing the pH from 2.5 to 7 decreased the complexation of the phthalates by 25%. As no evidence of a chemical reaction was obtained, the investigators concluded that the phthalates are adsorbed onto the surface of the fulvic acid by an unknown mechanism.

Giam, et al. (1976) reported a high affinity of DEHP for surfaces, and phthalates have been reported to accumulate on sediment samples (Jungclaus, et al., 1978). Morita, et al. (1974) reported that phthalates dissolved or suspended in water may be absorbed onto the sediment or may settle with other suspended material, resulting in phthalate-free water. They further suggested that the processes of sedimentation, uptake by aquatic animals and plants, and biodegradation probably determined the fate of phthalates in river water and that the actual river concentration of phthalates is dependent on an equilibrium between entry and removal from the water.

A number of investigators have reported the ability of phthalates to accumulate in food chains and in lipid-rich tissues of both plants and animals (Fishbein and Albro, 1972; Marx, 1972; Metcalf, et al., 1973; Mathur, 1974a). Numerous laboratory and ecosystem studies have documented the bioaccumulation and magnification of a number of phthalate esters in such aquatic organisms as the waterflea, scud, shrimp, guppy, snail and other fish (Mayer, et al., 1972; Metcalf, et al., 1973; Mayer and Sanders, 1973; Sanders, et al., 1973; Sanborn, et al., 1975; Booth, et al., 1977; Mayer, 1976). In his review, Peakall (1975) concluded that because of the fairly rapid metabolism of phthalates in fish and mammals, the largest concentrations of these esters are expected at intermediate points on the food chain, rather than at the end. Giam, et al., (1976) also suggested that phthalates may be readily metabolized in biota from the open ocean.

Continuous exposure of aquatic organisms to radiolabelled phthalates such as ^{14}C-DEHP, DOP, and DBP results in an initial rapid uptake and accumulation of radioactive residues (Mayer and Sanders, 1973; Sanders, et al., 1973). Sanborn, et al., (1975) investigated the fate of ^{14}C-labelled DOP in two model ecosystems utilizing a variety of organisms. At the end of a 33-day study in a terrestrial-aquatic ecosystem which contained DOP, algae contained the largest residues of DOP and the waterflea, the least, with intermediate values for mosquito fish, snails and mosquito larvae. The biomagnification values were reported as 28,500 for algae, 13,600 for snails, 9,400 for fish and mosquitoes, and 2,600 for waterfleas. In a three-day aquatic ecosystem, higher DOP residues were detected in all the tested organisms except for fish. In this system, waterfleas had the highest residue levels, and snails, fish and algae, the least. Magnification factors were 9,426 for waterfleas, 5,300 for mosquitoes, 660 for algae, 438 for snails and 1.16 for fish. The investigators suggested that the higher accumulation factors resulting from longer exposure indicated the persistence and accumulation of DOP.

Using the same 33-day model ecosystem with ^{14}C-DEHP, Metcalf, et al. (1973) and Booth, et al. (1977) reported magnification factors of 107,670 for mosquito larvae, 53,890 for algae, 21,480 for snails, and 130 for fish. Uptake studies conducted in this same experiment similarly demonstrated that the mosquito larvae accumulated the most DEHP and the aquatic plant Elodea canadensis, the least. Mayer and Sanders (1973) reported accumulation of DEHP residues in scuds at levels 3,600 times greater than in water during 14 days of continuous exposure (see Table IX), while in an earlier study Mayer, et al. (1972) reported an accumulation factor in scuds of 13,400 after the same length of exposure.

Table IX

Accumulation of ^{14}C-di-2-ethylhexyl phthalate by aquatic organisms

Organism	Water concentration, µg/l.	Accumulation factor after			
		1 day	3 days	7 days	14 days
Waterflea *(Daphnia magna)*	0.3	93	250	420	—
Scud *(Gammarus pseudolimnaeus)*	0.1	720	1,380	3,900	3,600
Midge *(Chironomus plumosus)*	0.3	270	330	350	—
Mayfly *(Hexagenia bilineata)*	0.1	210	250	575	—
Fathead minnow *(Pimephales promelas)*	1.9	135	245	369	458

Source: Mayer and Sanders, 1973

The dynamics of DBP accumulation in scud were also investigated in these same two studies. Mayer, et al. (1972) reported residue accumulations of DBP at 6,700 times the water concentration within 14 days, while the 1973 study by Mayer and Sanders yielded a value of 1,400 times the water concentration within the same time period (see Table X).

Table X

Accumulation of ^{14}C-di-n-butyl phthalate by aquatic invertebrates

Organism	Water concentration, µg/l.	Accumulation factor after 1 day	3 days	7 days	14 days
Waterflea *(Daphnia magna)*	0.08	170	280	400	400
Scud *(Gammarus pseudolimnaeus)*	0.10	360	780	1,350	1,400
Midge *(Chironomus plumosus)*	0.18	380	420	720	
Mayfly *(Hexagenia bilineata)*	0.08	130	230	430	

Source: Mayer and Sanders, 1973

Sanders, et al. (1973) studied the ability of aquatic organisms to accumulate DEHP and DBP. The values these investigators obtained for magnification factors (see Tables XI and XII) for DBP and DEHP are considerably higher than those obtained in other studies. Sanborn, et al. (1975) questioned these high values on the basis of their own work with DOP indicating that determination of accumulation factors using analyses of total radioactivity could lead to misleadingly high results. These authors believed that the DEHP magnification factors were probably considerably lower than those Sanders, et al. had reported. For example, Marx (1972) reported that Stalling, et al. have found accumulation factors of 350 to 3,900 times the water concentration for DBP and DEHP in organisms after seven days.

Table XI

"Biologic Magnification" of ^{14}C-Labelled Di-Ethylhexyl Phthalate From Water by Five Species of Aquatic Invertebrates

Organism	No. per sample	Water concentration (μg/1 ± SE[a])	Magnification factor[b] after (days)				
			1	3	7	14	21
Scud *Gammarus pseudolimnaeus*	18	0.1 ± 0.01	2800	5300	13600	13400	—
	18	62.8 ± 3.31[c]	30	100	116	270	260
Midge larvae *Chironomus plumosus*	18	0.3 ± 0.04	2400	2600	3100	—	—
Waterflea *Daphnia magna*	180	0.3 ± 0.04	1200	2500	5200	—	—
Mayfly *Hexagenia bilineata*	9	0.1 ± 0.01	850	1000	2300	—	—
Sowbug *Asellus brevicaudus*	4	1.9 ± 0.12[c]	—	—	80	71	70
	4	62.3 ± 3.31[c]	—	—	20	230	250

[a] Samples taken in triplicate snd expressed as mean ± SE ($P = 0.05$).

[b] The extracted radioactivity was assumed to be all ^{14}C-labelled di-ethylhexyl phthalate and the concentrations were derived from the original specific activity (1.64 mCi/mmole).

[c] Temperature = 25°C.

Source: Sanders, et al., 1973

Table XII

"Biologic Magnification" of ^{14}C-Labelled Di-n-Butyl Phthalate From Water By Six Species of Aquatic Invertebrates at 21°C

Organism	No. per sample	Water concentration (μg/1 ± SE[a])	Magnification factor[b] after (days)			
			1	3	7	14
Midge larvae *Chironomus plumosus*	18	0.18 ± 0.015	3500	3900	6600	—
Waterflea *Daphnia magna*	180	0.08 ± 0.005	2200	3500	5000	5000
Scud *Gammarus pseudolimnaeus*	18	0.10 ± 0.010	1700	3700	6500	6700
Mayfly *Hexagenia bilineata*	9	0.08 ± 0.001	500	980	1900	—
Glass shrimp *Palaemonetes kadiakensis*	9	0.08 ± 0.001	1500	5000	—	—
Damselfly *Ischnura verticalis*	9	0.10 ± 0.005	1000	1600	2700	—

[a] Samples taken in triplicate and expressed as mean value ± SE ($P = 0.05$).

[b] The extracted radioactivity was assumed to be all ^{14}C-labeled di-*n*-butyl phthalate and the concentrations were derived from the original specific activity (1.64 mCi/mmole).

Source: Sanders, et al., 1973

Sanders, et al. (1973) reported that with the exception of midge larvae, aquatic insects appeared to accumulate phthalate residues at a slower rate than crustaceans, and in general, DEHP was accumulated to a greater extent than DBP. There is also evidence to indicate that aquatic organisms concentrate the phthalates to a higher degree than do laboratory rodents (Tepper, 1973). Sanders, et al. (1973) found from their accumulation studies that the magnification of DEHP residues in scud was much lower when they were exposed to a higher phthalate concentration and increased water temperature. This suggested to these investigators that phthalate accumulation was favored in scud at low concentrations. Higher phthalate concentrations and increased water temperatures may stimulate metabolism and elimination and result in decreased magnification. They also suggested that the balance between accumulation and elimination is largely what determines the extent of magnification in an organism.

Mayer (1976) conducted a study in which fathead minnows were exposed to labelled DEHP for 56 days at concentrations ranging from 1.9 to 62 µg/l. Accumulation factors of 34 to 137 times the level in water were observed in 24 hours. These factors are in agreement with results reported by Metcalf, et al. (1973) in a study using guppies. Equilibria of ^{14}C-DEHP in the minnows were reached more slowly as the concentration of DEHP increased. Accumulation factors which ranged from 91 to 569 for DEHP and from 155 to 886 for total ^{14}C decreased as exposure concentration increased. This possibly indicated the induction of detoxifying enzymes in the liver with the ultimate effect of lower accumulation factors through increased degradation and elimination. As exposure concentrations were increased, the proportion of DEHP decreased and degradation products increased.

In earlier studies, Mayer and Sanders (1973) continuously exposed fathead minnows to ^{14}C-DEHP for 56 days. The accumulation factor of 458 measured after 14 days had increased to 1,380 by the time equilibrium was reached after 28 days of exposure. Once equilibrium was achieved no further residue accumulation was observed in the fish upon additional exposure. Similar results were obtained for DBP in the waterflea by Sanders, et al. (1973). After equilibrium was achieved in waterfleas on seven days of exposure, no further residue magnification was observed following an additional seven days exposure. In other work, Mayer, et al. (1972) reported residue levels of DEHP in fathead minnows to be only 28 times that found in water after a 28-day exposure.

The data from these studies demonstrate that phthalates are accumulated in the environment and undergo biomagnification in aquatic organisms. There are also indications that these compounds are biodegradable. Indeed, Morita, et al. (1974) have observed that aquatic animals and plants may play a significant role in the removal of phthalates from river water as will be discussed in the following section.

8. Environmental Degradation

In his review, Peakall (1975) commented that the usually slow leaching of phthalates from plastics in "terrestrial situations" can be accelerated by various environmental factors. For example, Decoste (1968) found ants feeding on plasticized wire insulation and Pazinski (1973) reported Streptomyces rubrireticuli growing on polyvinyl chloride material. The biodegradation of phthalates has been reported in laboratory cultures of pure or mixed microbial populations (Mathur, 1974b; Mathur and Rouatt, 1975; Engelhardt, et al., 1975; Keyser, et al., 1976; Perez, et al., 1977), in fresh water hydrosoil (Johnson and Lulves, 1975), and in river water and activated sludge (Saeger and Tucker, 1973 and 1976). Phthalate degradation has also been observed in organisms such as fish and snails (Mayer, et al., 1972; Mayer and Sanders, 1973; Sanders, et al., 1973; Metcalf, et al., 1973; Sanborn, et al., 1975; Booth, et al., 1977; Mayer, 1976). These studies and some general considerations on the degradation of phthalates in the environment are described briefly in the following paragraphs.

The available data on degradation and elimination indicate that phthalate esters with partially oxidized or short alkyl chains such as DBP are more easily biodegraded than long chain alkyl esters such as DEHP (Keyser, et al., 1976). In contrast, a laboratory study by Morita, et al. (1974) showed that DBP (because of its greater polarity and solubility) is more difficult to remove from water by complexing with chemicals such as alum than is DEHP. In model ecosystem studies, Sanborn, et al. (1975) also found that DEHP, possibly because of its greater hydrolytic stability arising from its branching, accumulated more than did DOP. Keyser and his colleagues (1976) commented that photochemical transformations of the phthalates may occur, but they found no detailed reports in the literature. They also stated that it is not certain how stable the phthalates are to hydrolysis, such as that catalyzed by clay minerals or other agents. It has been estimated (Mabey, personal communication) that, although phthalates in the environment can undergo uncatalyzed hydrolysis, the hydrolysis half-lives at pH 3-7 are greater than one year. If phthalates remain in solution (i.e., are not absorbed on particulates in aquatic systems) the hydrolysis half-lives at pH >8 may be less than one year. The hydrolysis half-lives at pH 1-3 will also be greater than one year.

In their reviews of the literature, Peakall (1975) and Mathur (1974a) reported that in early experiments undertaken to study the biodeterioration of plastics, phthalates were not utilized by 24 species of fungi, and DEHP and DOP were utilized only to a negligible degree by strains of *Aspergillus* and the bacteria *Pseudomonas* commonly found on degraded plastic films. Strains of the yeasts *Saccharomyces* and *Zygosaccharomyces* were similarly unable to utilize DOP and DEHP (Mathur, 1974a). In a multi-laboratory study it was determined that DIOP was also not utilized by any of 23 fungal isolates tested (Mathur, 1974a). Klausmeier and Jones (1960) found that DOP and DAP did not support the growth of microorganisms, and growth was scanty with DMP. Moderate growth was observed with DEP, DPP, DBP, and with butyl isodecyl, n-octyl n-decyl, and isooctyl isodecyl phthalates. Other reports providing evidence of the inability of microorganisms to utilize phthalates have been reviewed by Mathur (1974a).

There is evidence from more recent studies that the microbial degradation of phthalates does occur. Data from various studies indicate that mixed microbial populations appear to be the most effective in degrading the phthalates (Engelhardt, *et al*., 1975; Saeger and Tucker, 1976). Regardless of the particular organism(s) involved, the biodegradation of phthalates appears to proceed via common intermediates. Evidence for at least part of the scheme of microbial degradation proposed by Keyser, *et al*. (1976) (see Figure 1) has been obtained from virtually every recent study. The most common route of degradation of the diesters is via hydrolysis to the monoester (Engelhardt, *et al*., 1975). The most difficult step appears to be hydrolysis of the second ester moiety (Engelhardt, *et al*., 1975), and much less is known about the

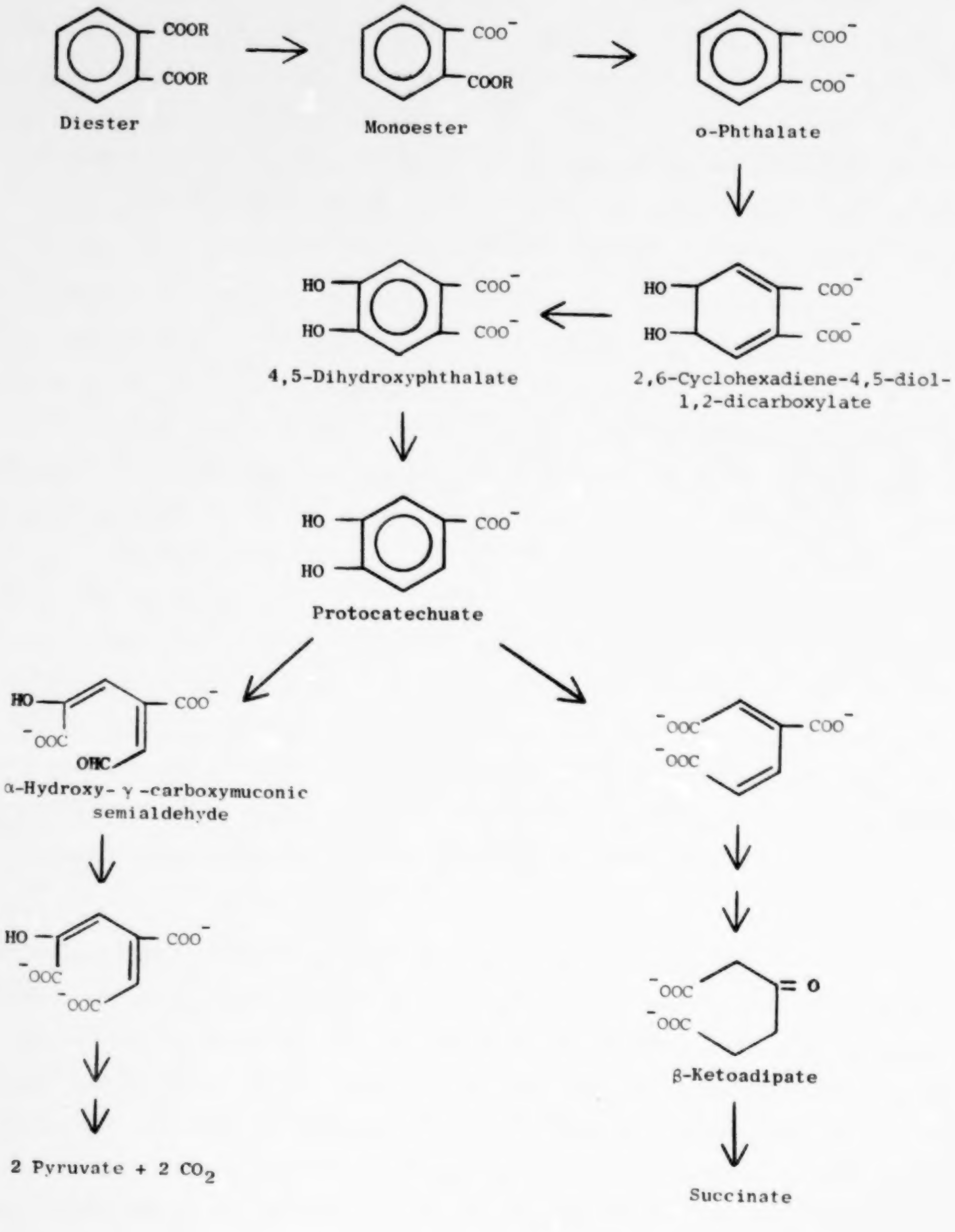

Figure 1: Proposed Scheme of Microbial Degradation

Source: Keyser, et al., 1976

degradation of this moiety (Keyser, *et al*., 1976). Bacterial degradation usually results in complete oxidation of the aromatic ring (Keyser, *et al*., 1976).

Perez, *et al*. (1977) isolated the bacterial strain *Enterobacter aerogenes* from old plastic tubing and found it capable of utilizing *DMP* as the sole carbon source. These bacteria, which are found in sewage, soil, water, dairy products and the human intestinal tract, utilized 67.4% of the chemical during a 41-day incubation. Engelhardt, *et al*. (1975) found that isolates of several soil bacteria and of the fungus *Penicillium lilacinum* grown with *DBP* as the carbon source formed the monoester within one to four weeks almost quantitatively as the only metabolite. They also found that the bacterial cells grown on *DBP* were able to utilize the monoester degradation product, phthalic acid and protocatechuic acid as carbon sources (see the proposed scheme in Figure 1). Because both phthalic acid and protocatechuic acid were utilized by these bacteria, it was suggested that the organisms degrade phthalic acid via 4,5-dihydroxy phthalic acid, protocatechuic acid, and cis,cis-β-carboxy muconic acid, (see Ribbons and Evans, 1960 for evidence of a similar pathway in soil *Pseudomonads*). *DIBP*, *DOP*, *DEHP*, and *MBP* were also able to support bacterial growth while *DMP* was utilized by only two of the bacteria. With each of the diesters, the corresponding monoester was detected as a degradation product. A somewhat different but unspecified mechanism of degradation was believed to occur in the *Penicillium* fungus, since several unidentified metabolites with an intact phthalic acid moiety were isolated from cultures growing on *DBP*, *DOP* and *DEHP*.

Mathur (1974b) reported that Eggins, *et al*. (1971) found four of 18 thermophilic fungi able to grow in a *DOP*-containing medium. In his own studies, Mathur (1974b) found *DOP* and *DEHP* to be utilized by soil microorganisms at 22° and 32°C, but not at 4° or 10°C. *DIBP* was degraded at all temperatures, but at a slower rate at the lower temperatures. A later study by Mathur and Rouatt (1975) demonstrated that *Serratia marcescens* Bizio (found in soil, water, and food), was capable of growth on *DEHP* and *DOP* at substrate concentrations of up to 2.5% and on *phthalic acid* at levels below 1.25%. No growth was detected using 2-

ethylhexanol as the substrate, but 0.8% DEHP was utilized to the extent of about 95% in three weeks. Phthalic acid was believed to be a primary product of the metabolism of DEHP and DOP.

Using cell extracts of Micrococcus grown on DMP, Keyser, et al. (1976) found that hydrolysis of DMP, DBP, and DEP readily occurred, with DEP hydrolyzed the most rapidly. Using Pseudomonas fluorescens PHK, they also determined that the dihydrodiol, 4,5-dihydro-4,5-dihydroxyphthalate, is a probable intermediary metabolite between o-phthalate and 4,5-dihydroxyphthalate. Nakazawa and Hayashi (1977) studied the degradation of phthalates in Pseudomonas testosteroni and found that it too was capable of degrading the phthalate anion via 4,5-dihydroxyphthalate and protocatechuate.

Limited work by Graham (1973) indicating the degradation of DEHP and BBP by a semi-continuous activated sludge system was expanded upon by Saeger and Tucker (1973 and 1976) who examined the degradation of phthalates in acclimated activated sludge and unacclimated river water. Using the Semi-Continuous Activated Sludge Biodegradation Test to examine sludge from a domestic sewage treatment plant, they found that phthalic acid, MBP, BPBG, and BBP were completely degraded to phthalic acid-related intermediates, while DEHP was degraded to the extent of 70 to 78%. BPBG and BBP also underwent complete degradation to water-soluble aromatic intermediates, which then underwent enzymatic ring cleavage to smaller nonaromatic molecules. In the River Die Away Test, which more closely simulates "real life" conditions, BPBG and BBP underwent degradation faster than the sulfonate control compound. DEHP and the mixed di (heptyl, nonyl, undecyl)phthalate also underwent degradation but at a slower rate (Saeger and Tucker, 1973). Saeger and Tucker (1976) also found that DUP was degraded to the extent of 45% when added to the activated sludge system at a rate of 5 mg/cycle while an additional rate of 20 mg/cycle decreased the degradation rate to 29%. In a separate test to measure the evolution of carbon dioxide, it was found that BBP, DEHP, and the mixed di(heptyl, nonyl, undecyl)phthalate were essentially completely degraded under the mild test conditions (Saeger and Tucker, 1976). The investigators concluded that the data on BBP and BPBG, indicating the conversion of phthalates to the monoesters and phthalic acid and ultimately to carbon dioxide and water, were in agreement with the bacterial data of Engelhardt, et al. (1975).

The data of Saeger and Tucker (1976) were also in basic agreement with the experiment of Johnson and Lulves (1975) who examined the degradation of DBP and DEHP in freshwater hydrosoil. Under aerobic conditions, 46% of labelled DBP was degraded to the monoester within 24 hours and almost 98% of all the activity had disappeared after five days. Under similar conditions, 14 days were required for 53% of labelled DEHP to disappear. Under anaerobic conditions, degradation of both esters was retarded. Almost 70% of the activity of DBP remained after five days of incubation; however, almost 98% of the labelled compound had disappeared from the soil after 30 days of incubation (hydrolysis of DBP, therefore, required twice as much time under anaerobic conditions and decarboxylation took six times longer). No significant degradation of ^{14}C-DEHP was observed even after 30 days. Following a one-day incubation, the major degradation product of DBP under either condition was identified as the monoester (46%) together with smaller amounts of phthalic acid and some unidentified compounds. Under anaerobic conditions, an increase in the monoester was observed after long incubation, but none of the more polar degradation products accumulated. The monoester of DEHP was also identified under aerobic conditions, but no other degradation products were found. Respirometry data indicated rapid decarboxylation of phthalic acid in hydrosoil. The authors proposed that under either aerobic or anaerobic conditions, diesters in hydrosoil are intially hydrolyzed at the ester linkage to form the monoester and the corresponding alcohol. The monoester is subsequently degraded primarily to phthalic acid, which may be decarboxylated to catechol or benzene. Because of the position of the radioactive label (on the carbonyl carbon), they were unable to obtain evidence suggestive of ring cleavage after ester hydrolysis.

In evaluating the work of Johnson and Lulves (1975), Keyser, et al. (1976) commented on the observation that the monoester and phthalate anion were completely degraded within 7 days in hydrosoil; whereas, only 50% of the ^{14}C was recovered from the diester during this same period.

Since about 50% of the diester was hydrolyzed to the monoester in one day, Keyser and his associates suggested that the phthalate diesters may partially inhibit their own biodegradation under some conditions.

Studies in aquatic organisms provide further evidence for the biodegradation of phthalates. In the model ecosystem studies of Sanborn, *et al*. (1975), analysis of water samples taken from both aquatic and terrestrial-aquatic systems (containing such organisms as algae, mosquito fish, snails, waterfleas and mosquito larvae) at three-day intervals demonstrated that *DOP* was rapidly degraded by the organisms in the study and was not detectable in water samples after 15 days. An approximate half-life of five days was estimated for *DOP* in water. Coupled with the decline in *DOP* in water was a rapid rise in the concentration of phthalic acid, which comprised 55-65% of the ether-extractable material after ten days. Also identified was the monoester which reached a maximum concentration on the sixth day. Transformation of the ester to polar metabolites was also indicated. After 12 days, the unextractable activity reached a maximum of 60% and remained constant for the duration of the experiment.

In the studies of Metcalf, *et al*. (1973) and Booth, *et al*. (1977) using ^{14}C-*DEHP* in the 33-day ecosystem, the concentration of radioactivity in the aquatic phase reached a peak of 0.031 ppm by the fifth day of the experiment, declining to 0.0077 ppm by the end of the study, indicating accumulation by the organisms. Only *DEHP* was found in algae and mosquito larvae, indicating little degradative ability by these organisms. The snail produced substantial quantities of the monoester, phthalic acid, and phthalic anhydride. Fish were the most active in metabolizing *DEHP*, with half the activity in the form of phthalic anhydride, presumably from phthalic acid. Studies of the uptake of *DEHP* by guppies revealed that a steady decline in activity was observed in the guppy, with total activity declining from 88.5% after one day to 37.1% after two days and to 16.8% after seven days. Polar metabolites increased from 11.5% after one day to 34.2% after two days and to 80.6% after seven days. Phthalic acid, which comprised 23.8% of the activity after two days, declined to 4.8% after seven days. Small amounts of phthalic anhydride also were identified.

A similar degradation pattern was observed in uncontaminated guppies, which had been fed waterfleas exposed to ^{14}C-DEHP for one day. The snail, clam, waterflea, and aquatic plant Elodea exhibited low degradative capacity. The snail still contained 86.6% of the initial concentration of DEHP after seven days, together with small amounts of the anhydride and an unknown metabolite. Metcalf, et al. (1973) proposed that the major degradative pathways appeared to be through hydrolysis of the ester group to produce the monoester, then phthalic acid, and then the anhydride.

Studies by Mayer and Sanders (1973) revealed that elimination of 50% of DEHP and its degradation products from minnows exposed to DEHP in their environmental water for 56 days occurred within seven days after they were placed in fresh water. In addition to the di- and monoesters, residues comprising 5 to 26% of the total activity were identified as free and conjugated phthalic acid and monoester. Mayer (1976) reported the half-life of DEHP in fathead minnows to be 12.2 days. Scuds exposed to DEHP for seven days and then transferred to fresh water retained only 20% of the radioactivity after four days in fresh water and only 6% after ten days. Waterfleas similarly exposed to DBP lost 50% of the radioactivity after three days in fresh water, and 75% after seven days. Stallings, et al. (1973) exposed channel catfish to 1 μg/l ^{14}C-DEHP for 24 hours and identified metabolites similar to those found in other organisms. They stated that the presence of appreciable amounts of the monoester in fish suggested that this metabolite was refractive to further degradation. Studies in vitro by these investigators using hepatic microsomes from channel catfish indicated that DBP was metabolized 16 times faster than DEHP. In vitro, formation of monoesters as well as of unidentified metabolites was observed. In experiments with microsomal enzyme inhibitors and cofactors, these investigators determined that, in this system, the monoester is not further degraded, and the unidentified metabolites are derived directly from the parent ester.

All the evidence summarized above indicates that the phthalate esters are biodegraded by a variety of organisms under laboratory and simulated environmental conditions, but Johnson and Lulves (1975) have commented that the fate of phthalate esters in the natural aquatic environment is still largely unknown.

C. Biological Effects

1. Ecological Hazards

a. Toxicity to Wildlife

(1) Acute Toxicity

Few toxic effects have been observed in birds, fish, and other aquatic organisms following exposure to alkyl phthalates. Driaze, et al. (1948) reported an oral LD_{50} value of 8.5 ml/g for DMP in chickens. The 96-hour LC_{50} values of DBP and DEHP in fish and crustaceans reported by Mayer and Sanders (1973) and Sanders, et al. (1973) are listed in Table XIII, and range from 0.73 mg/l for DBP in bluegills to more than 32 mg/l for DEHP in scud. The LC_{50} values for these compounds are approximately three orders of magnitude greater than the LC_{50} values of DDT in the same organisms, indicating a much lower level of toxicity for the alkyl phthalates.

Table XIII

96-Hour LC_{50} Values in Fish and Crustaceans
(Milligrams per Liter)

Organism	DBP	DEHP
Fathead minnow	1.30	>10
Bluegill	0.73	>10
Channel catfish	2.91	>10
Rainbow trout	6.47	>10
Scud	2.10	>32
Crayfish	>10.00	>10

Source: Mayer and Sanders, 1973 plus Sanders, et al., for data on scud

An exception to the low toxicity has been reported for DBP, which has been observed to exert a toxic effect on shrimp larvae at a concentration of 3.7×10^{-5}M, as evidenced by an increased mortality rate compared to controls (Sugawara, 1974).

(2) Reproductive System Effects

Alkyl phthalates have been reported to induce significant adverse reproductive effects in chickens and aquatic organisms. Bower, et al. (1970) injected eight phthalates into the yolk sacs of groups of developing chick embryos in volumes ranging from 0.025 to 0.10 ml, and determined the toxicity of the compounds to the embryos as evidenced by the number of embryos not surviving. DMEP at a dose of 0.1 ml exhibited the highest embryotoxicity, since 46/50 (92%) of the embryos died before hatching, compared to 45 and 53% mortality with sesame oil- and Crisco oil-treated controls, respectively.

Mayer, *et al*. (1972) exposed zebra fish to a diet containing 50 or 100 µg/g DEHP. As many as 88% of the offspring died before they began foraging, compared to 50% among controls. In addition, the progeny of the phthalate-treated fish all died in tetany, while tetany was not observed among progeny of controls.

Sanders, *et al*. (1973) exposed waterfleas to DEHP at concentrations of 3, 10, and 30 µg/l for a complete life cycle of 21 days. The chemical reduced reproduction by 60, 70, and 83% at the three doses, respectively. The concentrations found to induce these decreases in reproduction were 1/700 to 1/11000 the LC_{50} concentrations. In another study, DBP at three concentrations (1,8, and 19 x 10^{-5}M) and DEHP at the highest concentration tested (28 x 10^{-5}M) significantly reduced the number of brine shrimp larvae hatched/mg eggs (Sugawara, 1974).

Although acute toxicity studies indicate a very low order of toxicity for these esters to birds and aquatic organisms, it has been hypothesized that the adverse reproductive effects of the chemicals at very low dose levels could cause a serious imbalance in the food chain (Sanders, *et al*., 1973).

b. Toxicity to Plants

DBP and DIBP have been reported to induce toxic effects such as symptoms of chlorosis in egg plant, cucumber, tomato, pepper, and strawberry plants following exposure of the plants to vapors of the esters (Inden and Tachibana, 1975). DBP and DOP have been reported to inhibit the elongation of wheat coleoptile, as well as to delay the aging process in *Rumex obtusifolius* leaves (Gudin and Harada, 1974).

c. Toxicity to Microorganisms

The toxicity of the alkyl phthalates to various microorganisms appears to be very low. Recent studies indicate the ability of microorganisms to grow in the presence of the chemicals, and in some cases, to utilize the esters as their sole carbon source (see Section III B.8).

2. Effects Related to Human Health Hazards

a. Carcinogenicity*

In the several animal carcinogenicity tests of alkyl phthalates reported in the literature, no carcinogenic effects related to the treatments have been observed. In one study, EPEG was administered orally in the diet to 150 rats for two years at dose levels ranging from 0.05 to 5.0%. Six rats were reported to have tumors but the investigators did not attribute them to the treatment. At the highest dose level, 100% mortality by 55 weeks was reported (Hodge, et al., 1953; Shubik and Hartwell, 1957).

Carpenter, et al. (1953; Shubik and Hartwell, 1957) investigated DEHP by oral administration of 0.04 to 0.4% of the chemical in the diet for two years to 192 Sherman rats. Nine treated rats were reported to have neoplasms (which were not characterized pathologically); this tumor incidence was not considered by the investigators to be significant. In a different study, Harris, et al. (1956; Shubik and Hartwell, 1969) administered the chemical in the diet to 172 weanling Albino-Wistar rats for two years at dose levels of 0.1 and 0.5%. A total of three fibroliposarcomas were observed, that were considered by the investigators to be unrelated to the treatment. Few treated or control animals were reported to have survived the total two-year testing period.

In their study of six phthalates applied to mouse skin as 5 and 10% acetone solutions, Wynder and Hoffmann (1964) observed that only DAP induced some hyperplastic reaction on mouse skin. No tumor-promoting activity was observed after five months with DBP or DOP applied to mouse skin that had been initiated with 300 μg of the carcinogen 7,12-dimethylbenz(a)anthracene.

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* The alkyl phthalates BBP, DAP and DEHP are currently on test in the NCI Carcinogenesis Bioassay Program.

In a recent short-term study using the test for induction of pulmonary lung adenomas developed by Shimkin (Shimkin and Stoner, 1975), BBP* was injected intraperitoneally into strain A/St male mice at doses of 160, 400, and 800 mg/kg, three times weekly for eight weeks. No statistically significant increase in the incidence of lung tumors over controls was observed (Theiss, 1977).

In several other experiments, no carcinogenic effects of alkyl phthalates were observed. These tests were the following:

1) DBP (Smith, 1953; Shubik and Hartwell, 1957; Lefaux, 1968), dibutoxyethyl phthalate (Mallette and von Haam, 1952; Shubik and Hartwell, 1957), dicapryl phthalate (Mallette and von Haam, 1952; Shubik and Hartwell, 1957) or DCHP (Lefaux, 1968) in rats;

2) DMP in rats (White and Edwards, 1942; Draize, *et al.*, 1948; Hartwell, 1951; Shubik and Hartwell, 1957), chickens, mice, guinea pigs (Draize, *et al.*, 1948; Shubik and Hartwell, 1957), and rabbits (Draize, *et al.*, 1948; Haag, *et al.*, 1948 and 1950; Shubik and Hartwell, 1957);

3) DEHP in dogs (Carpenter, *et al.*, 1953; Harris, *et al.*, 1956; Shubik and Hartwell, 1957 and 1969), rats (Shubik and Hartwell, 1969), and guinea pigs (Carpenter, *et al.*, 1953; Shubik and Hartwell, 1957); or

4) EPEG in rats and dogs (Hodge, *et al.*, 1953; Shubik and Hartwell, 1957).

All these experiments, however, were of a shorter duration and were carried out with fewer test animals than are usually considered adequate for a carcinogenicity test.

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* The identity of the chemical tested in this study is not certain, as the structure given for BBP is actually that of butyl benzyl terephthalate in which the ester moieties are *para*- to each other.

b. Mutagenicity

Although various alkyl phthalates have been tested for mutagenicity and induction of gene damage (EMIC, 1978), the only demonstrated activities were the induction of dominant lethal mutations in male mice by DEHP and by DMEP. In these experiments, groups of male mice were given single intraperitoneal injections of one of the two chemicals at three dose levels (12.78, 19.17, and 25.56 ml/kg DEHP, and 1.19, 1.79, and 2.38 ml/kg DMEP), and were subsequently mated with two females each week for twelve weeks. Mutagenic effects were evidenced by decreased implants/pregnancy and increased early fetal deaths, both at the highest dose levels during the first three weeks after exposure of the males to the chemicals (Dillingham and Autian, 1973; Singh, 1974). It should be noted that the adequacy of these tests is limited by the small numbers of animals treated (10 per group) and the lack of dose-response. Also, the intraperitoneal route of administration may not be relevant to determination of human health hazards from phthalates.

DMP was reported by Yurchenko (1977) to induce chromosome aberrations in regenerating hepatocytes of rats receiving repeated skin applications of the chemical, but no data or experimental details were available.

Alkyl phthalates were also tested in the following mutagenicity and chromosome-damaging tests, but no significant adverse effects were reported. Stenchever, *et al.* (1976) reported that DEHP induced no significant increase in chromosome aberrations *in vitro* in human leukocytes from four subjects at four dose levels, or in lung cells of a single human fetus at one dose level *in vitro*. DEP, DBP, DEHP, and BPBG were also reported to not induce significant chromosome aberrations in Chinese hamster cells *in vitro* at several dose levels (Ishidate and Odashima, 1977; Omori, 1976; Abe and Sasaki, 1977), although the incidence of sister chromatid exchanges in these cells was slightly elevated in the presence of DEHP and DBP (Abe and Sasaki, 1977).

DEP, DBP, DOP, BBP, DCHP, EPEG, BPBG, dihexyl, diheptyl, di(isoheptyl, isononyl), di(octyl, decyl), and diisodecyl phthalates were tested in microbial assays such as induction of point mutations in *Escherichia coli* and *Salmonella typhimurium*, and tests of the potential of a chemical for inducing DNA damage in strains of *Bacilus subtilis* and *E. coli*. The chemicals were reported to be inactive in these assays, but no experimental data were given (Kurata, 1975; Szybalski, 1958; Yagi, *et al*., 1976).

c. *Teratogenicity*

Alkyl phthalates have been reported to exert teratogenic effects in rats, mice, and chickens. Singh, *et al*. (1972) tested *DMP*, *DMEP*, *DEP*, *DBP*, *DIBP*, *BPBG*, *DOP*, and *DEHP* in female rats, administering intraperitoneal injections of the chemicals on days 5, 10, and 15 of gestation. The first six chemicals were given in doses of 1/10, 1/5, and 1/3 the LD_{50} levels, and the latter two were administered at dose levels of 5 and 10 ml/kg. The females were then killed before the end of pregnancy, and the fetuses were examined. All of the esters exhibited teratogenic effects, such as resorptions, decreased fetal size, fetal death, gross abnormalities, and skeletal malformations, although the degree of potency varied among compounds. The more water-soluble chemicals exerted stronger effects. *DMEP* and *DMP* were the most potent teratogens, inducing high rates of resorption, as well as absence of eyes, absence of tail, twisted hind legs, elongated and fused ribs, and incomplete bone development in skull and legs. *DEP*, *DBP*, *DIBP*, and *BPBG* treatment resulted in the skeletal abnormalities, and the middle dose of *DIBP* also resulted in the absence of eyes in two dead fetuses. Grossly malformed fetuses, especially twisted hind legs, were seen in groups treated with *DOP*. Effects of *DEHP* were seen only at the higher dose level, and consisted of one fetus with twisted hind legs, and 9/41 with hemangiomas of the legs. Yagi, *et al*. (1976) reported a significant incidence of external and skeletal malformations in the fetuses of mice treated with *DEHP*. Onda, *et al*. (1974) reported that the formation of renal cysts was increased in the offspring of mice fed *DBP* and *DEHP*.

Bower, *et al*. (1970) tested the teratogenicity of *BBP*, *DBP*, *DEP*, *DOP*, *DMEP*, *dibutoxyethyl*, *octyl isodecyl*, and *octyl decyl phthalates* in chick embryos. *Dibutoxyethyl phthalate* induced the most potent teratogenic effect. Chicks exposed to the chemical as embryos had defects such as neuromuscular abnormalities in which the chicks could not stand and demonstrated odd positioning of the legs, crania bifida, absence of eyes, malformation of the upper beak, grossly enlarged eye due to the absence of a normal orbit in the skull, and absence of the cornea. Exposure of embryos to DMEP and octyl isodecyl phthalate resulted in the neuromuscular abnormalities which included lack of normal coordination, and one chick exposed to DEP had a severe malrotation of the left leg. Guess, et al. (1967) reported deformed legs and neurological abnormalities in chicks exposed to butyl octyl or butyl decyl phthalates as embryos, and Haberman, et al. (1968) reported neurological defects in chicks following exposure to DOP, butyl octyl, and octyl isodecyl phthalates.

d. Systemic Toxicity

Alkyl phthalates evidence very low acute toxicity in mammals, ranging from 2.4 g/kg (rat, oral) for DMP to >100 g/kg (rat, oral) for DNP. The LD_{50} values for a number of the esters in several mammalian and one avian species by various routes of administration are listed in Table XIV. In general, the toxicity of these compounds decreases with increasing chain length of the ester.

In numerous studies, administration of single oral doses of various phthalate esters to humans and animals has produced very few toxic effects. For example, the only toxic effect reported by Shaffer, et al. (1945) in two humans ingesting 5 or 10 g DEHP was diarrhea. Lefaux (1968) reported nausea, vertigo, hepatitis, and toxic nephritis in a human ingesting 10 g DBP, but no after-effects were observed within two weeks. The only toxic effect reported in rats receiving 110 g/kg DEHP and in rats and mice ingesting 20 g/kg di(heptyl, nonyl) phthalate was diarrhea (Hodge, 1943; Gaunt, et al., 1968), and in rats receiving 5-10 g/kg diisononyl phthalate was oily fur (Livingston, 1976). Dermal application of various phthalates to rabbits and guinea pigs has been found to produce very low lethal toxicity from absorption (3-20 g/kg).

TABLE XIV

LD_{50} Values of Some Alkyl Phthalates

PHTHALATE ESTER	SPECIES	ROUTE	LD_{50}(g/kg)	REFERENCES
Dimethyl	Rat	Oral	2.4-6.9	Patty,1967a, Lehman, 1955
		IP	3.38*	Singh, et al., 1972
	Mouse	Oral	7.2	Lehman, 1955
		IP	3.98	Lawrence, et al., 1975
	Guinea pig	Oral	2.4	Lehman, 1955
	Rabbit	Oral	4.4	Lehman, 1955
		Dermal	10.0	Patty, 1967a
Diethyl	Rat	Oral	8.2*	Tyson, unpublished, 1972
		IP	5.06*	Singh, et al., 1972
	Mouse	IP	3.22	Lawrence, et al., 1975
	Rabbit	Oral	1.0	Patty, 1967a
Di(methoxyethyl)	Rat	Oral	4.4	Patty, 1967a
		IP	3.7	Calley, et al., 1966
	Mouse	Oral	3.2-6.4	Patty, 1967a
		IP	2.5	Calley, et al., 1966
	Guinea pig	Oral	1.6-3.2	Patty, 1967a
		Dermal	10.0	Patty, 1967a
Di-n-propyl	Mouse	IP	<1.25	Calley, et al., 1966
Diallyl	Rat	Oral	1.7	Patty, 1967a
	Mouse	IP	0.7	Patty, 1967a
	Rabbit	Oral	1.7	Patty, 1967a
		Dermal	3.4*	Patty, 1967a
Diisopropyl	Mouse	IP	<1.25	Calley, et al., 1966
Dibutyl	Rat	Oral	8-12	Smith, 1953; W.R. Grace, & Co., 1948
		IP	3.1*	Singh, et al., 1972
		IM	8.0	Patty, 1967a
		SC	<6.2	Kowalski & Bassendowsa, 1965
		Inh	0.7-0.9**	Spasovski, 1964
	Mouse	Oral	8	Smith, 1953
		IP	3.57	Lawrence, et al., 1975
	Rabbit	Dermal	20.0*	Patty, 1967a
Diisobutyl	Rat	Oral	20-25	Patty, 1967a
		IP	3.75	Singh, et al., 1972
	Mouse	Oral	12.8	Patty, 1967a
		IP	3.99	Lawrence, et al., 1975
	Guinea pig	Dermal	10.0*	Patty, et al., 1967a

TABLE XIV (Continued)

PHTHALATE ESTER	SPECIES	ROUTE	LD_{50} (g/kg)	REFERENCES
Butyl phthalyl butyl glycolate	Rat	Oral	14.6*	Patty, 1967a
		IP	6.89	Singh, et al., 1972
	Mouse	IP	6.88	Lawrence, et al., 1975
Dihexyl	Rat	Oral	30.0	Patty, 1967a
	Rabbit	Dermal	20.0*	Patty, 1967a
Dicyclohexyl	Rat	Oral	30.0*	Lefaux, 1968
Dioctyl	Rat	Oral	30.0	Radeva & Dinoeva, 1966
		IP	50.0*	Singh, et al., 1972
	Mouse	Oral	13.0	Patty, 1967a
		IP	65.7	Lawrence, et al., 1975
	Guinea pig	Dermal	5.0*	Patty, 1967a
Diisooctyl	Rat	Oral	22.6*	W.R. Grace & Co., 1948
Di(2-ethylhexyl)	Rat	Oral	26-34	Patty, 1967a; Hodge, 1943
		IP	50.0*	Singh, et al., 1972
	Mouse	Oral	34.0*	Union Carbide Corp., unpublished
		IP	38.4*	Lawrence, et al., 1975
	Rabbit	Oral	33.9	Patty, 1967a
	Guinea pig	Oral	26.3	Union Carbide Corp., unpublished
		Dermal	10.0	Patty, 1967a
Butyl benzyl	Rat	Oral	4.0	Mallette & Von Haam, 1952
		IP	1.8	Mallette & Von Haam, 1952
	Mouse	IP	3.2	Calley, et al., 1966
Dicapryl	Mouse	IP	14.2	Calley, et al., 1966
Dinonyl	Rat	Oral	2.0	Patty, 1967a
	Mouse	IP	>100	Lawrence, et al., 1975
Diisononyl	Rat	Oral	>10	Livingston, unpublished
Diisodecyl	Rat	Oral	>64	Smyth, et al., 1962
	Mouse	IP	>100	Lawrence, et al., 1975
Ditridecyl	Rat	Oral	>64	Smyth, et al., 1962
Butyl octyl	Rat	Oral	>63*	W.R. Grace & Co., 1948
Butyl decyl	Rat	Oral	20.8*	Smyth, et al., 1969
Hexyl decyl	Rat	Oral	49.4*	Smyth, et al., 1969
n-Hexyl n-octyl n-decyl	Rat	Oral	45.2*	W.R. Grace & Co., 1948

TABLE XIV (Continued)

PHTHALATE ESTER	SPECIES	ROUTE	LD_{50} (g/kg)	REFERENCES
Heptyl nonyl	Rat	Oral	>19.3	Brown, et al., 1970
	Mouse	Oral	>19.3	Brown, et al., 1970
Heptyl nonyl undecyl	Rat	Oral	>20	Brown, et al., 1970
	Mouse	Oral	>20	Brown, et al., 1970
Octyl decyl	Rat	Oral	45.2*	Smyth, et al., 1969
2-Ethylhexyl benzyl	Rat	Oral	60.3	Younger, unpublished
Nonyl undecyl	Rat	Oral	>19.7	Brown, et al., 1970
	Mouse	Oral	>19.7	Brown, et al., 1970

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*= ml/kg
**= mg/l

Experiments involving inhalational exposure of the phthalate esters to animals have also indicated few toxic effects (Autian, 1973).

In an epidemiological study of 147 workers exposed to phthalate plasticizers in factory air for 1/2 to 19 years, hypertensive reactions were observed in 28.3% of the subjects, and hypertensive disease in 6% of the workers. Slightly decreased levels of platelets and leukocytes, hemoglobin, and the blood color index, as well as slight reticulocytosis, enhanced rate of erythrocyte sedimentation among females, and moderate hyperbilirubinemia were also observed (Milkov, et al., 1973). It should be noted that the workers were also exposed to very low levels of other chemicals such as vinyl chloride, carbon monoxide, and hydrogen chloride, but the major contaminants of air samples within the factory were the phthalates.

A number of oral and inhalational subacute and chronic toxicity studies of phthalate esters have been conducted in rats, mice, rabbits, guinea pigs, and dogs. These studies have indicated a very low order of toxicity of these chemicals to animals. Decreased rates of weight gain and increased liver and kidney weights at high oral dose levels (>200 mg/kg/day DEHP, for example) are the only effects commonly noted by investigators (Carpenter, et al., 1953). In one dog and in rats given repeated oral doses of C_7 to C_{11} alkyl phthalates, Carpenter, et al. (1953) and Brown, et al. (1970) have detected vacuolization in liver cells from fatty deposits in the liver. Fatty vacuolization in the kidney of the dog was also observed.

There is some evidence to suggest that alkyl phthalates have a cumulative toxic effect. Lawrence, et al. (1975) found that following five intraperitoneal injections per week of several phthalates in mice, the LD_{50} values decreased over time. For example, the acute LD_{50} of DEHP was found to be 38.35 ml/kg, the calculated LD_{50} after one week was 6.40 ml/kg, and after 10 weeks was 1.37 ml/kg.

Seth, et al. (1976) and Cater, et al. (1976, 1977) have reported testicular atrophy in rats following three intraperitoneal injections of 5 ml/kg DEHP or daily oral doses of 2 g/kg DBP. A significant decrease in testes weights was noted, and histopathological examination revealed a decrease in spermatocytes and spermatogonia, as well as degenerated tubules and vacuolization in the cytoplasm of spermatogonial cells.

The phthalate esters also appear to exert adverse effects on reproduction in female rats. Singh, et al. (1972) administered DMP, DMEP, DEP, DBP, DIBP, BPBG, DOP, and DEHP to pregnant rats on days 5, 10, and 15 of gestation. The first six compounds were given at dose levels of 1/10, 1/5, and 1/3 of the LD_{50} values, and the last two were given at dose levels of 5 and 10 ml/kg. The compounds varied in the number of resorptions and fetal deaths induced, with DMEP, the most embryotoxic compound, inducing 89.7 and 96.5% resorptions at the two higher doses, compared to 6-11% among water, saline, or cottonseed oil controls. Fetal deaths appeared to be induced only by DMP, DMEP, and DIBP. In another study, DEHP has also been reported to induce fetal deaths in mice (Yagi, et al., 1976).

It has been suggested that chronic inhalational exposure of animals to high concentrations of DEP may cause an irritant response (Patty, 1967b). In more recent studies by Lawrence, et al. (1975) in which groups of mice were exposed to air which was virtually saturated with DEHP and DOP vapors for two hours/day, three days/week, for 4-16 weeks, no adverse toxicological or histological effects were found.

DMP may cause central nervous system depression in animals exposed by inhalation over long periods of time (Autian, 1973).

Various effects of phthalates on the blood chemistry and enzyme levels in exposed animals have been reported. DEHP fed in the diet at levels of 0.5, 2, or 4% to groups of rats and mice for 1 or 4 weeks significantly reduced the serum cholesterol and triglyceride levels, and the authors associated this effect with observed increases in hepatic catalase and carnitive acetyltransferase activities (Reddy, et al., 1976). Lake, et al. (1975) associated liver weight gain in rats induced by DEHP with decreased activities of microsomal glucose-6-phosphatase, aniline 4-hydroxylase, and mitochondrial succinate dehydrogenase, and Inouye, et al. (1978) have reported results which suggest that DBP uncouples oxidative phosphorylation in vitro. Piekacz (1971) reported a statistically significant increase in serum alanine aminotransferase in rats fed DOP at 1 and 5% of the diet for three months, and a significant increase in both alanine and asparagine aminotransferases in rats fed the chemical as 1% of the diet for one year. Dvoskin, et al. (1969) detected a transient increase in gamma globulin and alterations in phagocytic activity of neutrophils in rats exposed by inhalation to 0.2 or 0.4 mg/m^3 DBP for 2.5 months.

Several phthalate esters have been tested for their effect on hexobarbital- or pentobarbitone-induced sleeping time in mice and rats. DEHP has been reported to prolong barbituate-induced sleeping time in rats and mice (Rubin and Jaeger, 1973; Lawrence, et al., 1975; Swinyard, et al., 1976; Seth, et al., 1977), although Hidaka, et al. (1977) reported a decrease in hexobarbital-induced sleeping time in immature female mice. Lawrence, et al. (1975) also reported that DMP, DBP, DOP, DMEP, and EPEG prolonged pentobarbital-induced sleeping time in rats. The effect of DEP was equivocal, and DIBP decreased the drug-induced sleeping time. BPBG also was reported to prolong the barbituate effect (Rubin and Jaeger, 1973).

e. Dermatological and Sensitization Studies

Alkyl phthalates have been reported to be essentially non-irritating following dermal application to humans and most animals, and the compounds do not appear to exhibit sensitizing potential (Autian, 1973), but intradermal injections of the esters in rabbits have been reported to produce significant irritant responses. Some of the relevant studies reported in the literature are summarized in the following paragraphs.

Following 20 daily applications of 100 mg DBP, BBP, DOP, and higher ester phthalates to the skin of guinea pigs, Dueva and Aldyreva (1966) reported minor irritation to the reticuloendothelial cells of the skin only with the higher molecular weight compounds. Lawrence, et al. (1975) tested DMP, DEP, DBP, DIBP, DOP, DEHP, DNP, DIDP, DUP, DMEP, EPEG, and BPBG as irritants by applying them to the eyes of rabbits. No obvious irritation was observed for up to 48 hours after application.

In contrast, the investigators tested the same group of compounds for primary irritation by intradermal injection of the undiluted chemical into rabbits followed by injection of a dye which will concentrate in an inflamed region, and found DMP, DEP, and DMEP to induce a significant degree of irritation. In a similar study in which phthalate esters were injected as a suspension in 3% saline acacia solution, Calley, *et al.* (1966) reported marked irritant responses to DMP, DEP, and DEHP, moderate responses to DBP, DIBP, DMEP, and BBP, and mild response to dicapryl phthalate.

f. Neurotoxicity

Neurotoxic effects of alkyl phthalates were observed in an epidemiological study of 147 workers exposed to phthalate plasticizers used in the manufacture of artificial leather and films that were based on polyvinylchloride resins. Although the workers were exposed to very low levels of other chemicals such as vinyl chloride, carbon monoxide, and hydrogen chloride, the major contaminants of air samples within the factory were the phthalates; in many cases the other chemicals were not even detected. The duration of exposure of workers to the phthalates ranged from 1/2 to 19 years, with 93 workers exposed for more than six years. Forty-seven workers (32%) were found to have polyneuritis, and the incidence was higher among workers exposed for longer periods of time. The main symptoms of the inflammatory disease were pain and numbness in the extremities, depression of tendon reflexes, as well as some cases of slight paralysis, degeneration, and fasciculation. In addition, 22 workers (15%) were reported to have functional disturbances of the nervous system.

Workers exposed to the plasticizers also evidenced decreased sensitivity to pain (66.7%), decreased sensitivity to vibrations (33.8%), and depression of both vestibulosomatic and olfactory excitability (78, and 50 to 82%, respectively) (Milkov, *et al.*, 1973).

g. Behavioral Toxicity

In one study, DEHP appeared to depress two different activities in rats. One group of animals had surgically implanted electrodes in the hypothalmic pleasure center in the brain, so that the animals could receive a pleasurable stimulus by pressing a bar. Two hours after an intraperitoneal injection of 500 mg DEHP in saline acacia solution, the rate of bar pressing was reduced to 30% of the untreated control rate, while the rate among vehicle-treated animals was slightly lower than controls (90% of the untreated control rate). The second group of rats were metered for spontaneous running activity on a wheel during a 24-hour period. Rats were given a single injection of 500 mg DEHP in saline acacia solution, and the investigators observed that the activity of vehicle-treated animals was only 60% of the activity of untreated controls, while the activity of phthalate-treated animals was essentially completely inhibited (5% of untreated control rate). The investigators noted that although activity of the rats was decreased in these two studies by DEHP, the animals did not seem to be anesthesized, but were reasonably alert in response to outside stimuli (Rubin and Jaeger, 1973).

h. Metabolism

(1) Pharmacokinetics and Distribution

Alkyl phthalates are absorbed from the gastrointestinal tract, intraperitoneal cavity, and skin, as evidenced by their detection in tissues such as liver and lungs following oral, intraperitoneal, or dermal administration to animals (Autian, 1973). Daniel and Bratt (1974) found that approximately half of an oral dose of DEHP was absorbed in rats, the other half being recovered in the feces. Dermal absorption of the phthalate esters appears to increase with decreasing molecular weight (Autian, 1973).

The phthalates are removed from the blood rapidly, and the rate of disappearance follows a biphasic pattern with a short initial half-time of disappearance and a slower second phase. For example, Schulz and Rubin (1973) measured the initial half-time ($T_{\frac{1}{2}}\alpha$) of disappearance of DEHP in rats given an intravenous injection of 0.1 mg/kg to be 4.5 minutes, followed by a second half-time ($T_{\frac{1}{2}}\beta$) of 22 minutes. The rate of disappearance appears to increase as the dose level increases; the initial half-time after a dose of 200 mg/kg DEHP was 9 minutes.

These esters are widely distributed throughout the body. For example, Schulz and Rubin (1973) reported that one hour after rats were given an intravenous dose of 200 mg/kg of radioactively-labelled DEHP, 5% or more of the dose was detected in the liver, carcass, and spleen, with lower levels present in the lungs, stomach and small intestines, kidney, heart, and fat deposits, as well as trace amounts in the thymus, brain, and testes. Several studies have indicated that the esters are distributed mainly to the liver; Daniel and Bratt (1974) measured 38% of a 600 mg/kg intravenous dose of DEHP in the liver of rats after two hours, with 11% of the initial dose remaining after 48 hours. Distribution of phthalate esters to the lungs is highly variable, and appears to depend on the particle size of the chemical preparation. Schulz and Rubin (1973), for example, used DEHP in bovine serum albumin solution which was sonicated to give a true solution, and they detected only low levels of the labelled chemical in the lungs of rats. In contrast, Daniel and Bratt (1974) used an emulsion of the compound in oleic acid, and detected 26% of the dose (600 mg/kg, IV) in the lungs of rats after two hours, with 8.5% of the dose remaining after 48 hours.

Daniel and Bratt (1974) reported that DEHP accumulated in the body tissues of animals fed a diet containing the chemical over a number of weeks, but the chemical reached a dose-dependent equilibrium tissue concentration within 1-2 weeks. When the ester was removed from the diet, its tissue concentration declined to a negligible level in 3-5 weeks. For example, following administration of a diet containing 1000 ppm labelled DEHP to rats, steady-state concentrations of the compound in different tissues were: 40-50 ppm, liver; 7-9 ppm, fat; 1-6 ppm, heart; and <1 ppm, brain. At a level of 5000 ppm in the diet, the concentrations were: 120 ppm, liver; 80 ppm, fat; 15-20 ppm, heart; and 2-3 ppm, brain. When the animals were returned to a normal diet, the half-time of disappearance of the labelled compound from the liver was 1-2 days, and from the fat, 3-5 days.

Virtually all of the radioactivity from a single oral dose of ^{14}C-DEHP given to rats was recovered within seven days, distributed nearly equally between the urine and feces (Daniel and Bratt, 1974). When Schulz and Rubin (1973) injected the labelled ester intravenously in rats, approximately 17% of the dose was detected in the feces 24 hours after injection, indicating that the chemical is excreted in the bile.

(2) Metabolic Modification

The initial stage of metabolism of phthalate esters by humans and animals involving hydrolysis to the monoester appears to be the same as that by fish and microorganisms (see Section B.8). The studies summarized below support the currently postulated mechanism of subsequent ω- and (ω-1) oxidation of the remaining alkyl chain.

Albro, et al. (1973) have studied the metabolites of DEHP in the urine of rats receiving one or two oral doses of 0.2 ml of the radioactively-labelled compound. Four main metabolites were detected, all of which were derivatives of monoethylhexyl phthalate, and these four compounds with the percentages detected are shown in the metabolic scheme below (Figure 2). The compounds result from ω- or (ω-1)-oxidation of the remaining monoethylhexyl ester. These reactions are presumed to occur in the hepatic smooth endoplasmic reticulum, catalyzed by NADPH-dependent enzymes (Gillete, 1966). Following ω-oxidation, compound III may then undergo β-oxidation to yield compound IV. Hydrolysis of the parent compound to the monoester may be catalyzed by pancreatic lipase, since Daniel and Bratt (1974) found that when DEHP was incubated with rat pancreatic lipase in vitro, 67% of the dose was hydrolyzed to monoethylhexyl phthalate in one hour, and 77% had been hydrolyzed in five hours. Hydrolysis by a rat-liver homogenate was also detected, but to a lesser extent (8% hydrolysis after one hour). Albro and co-workers (1973) detected no DEHP in the urine, and only 2.8% of the dose was recovered as phthalic acid. The investigators also detected no glycine or glucuronic acid conjugates of the parent compound or any of its metabolites.

In a similar study, Albro and Moore (1974) investigated the metabolites of DMP, DBP, and DOP in the urine of rats given the chemicals

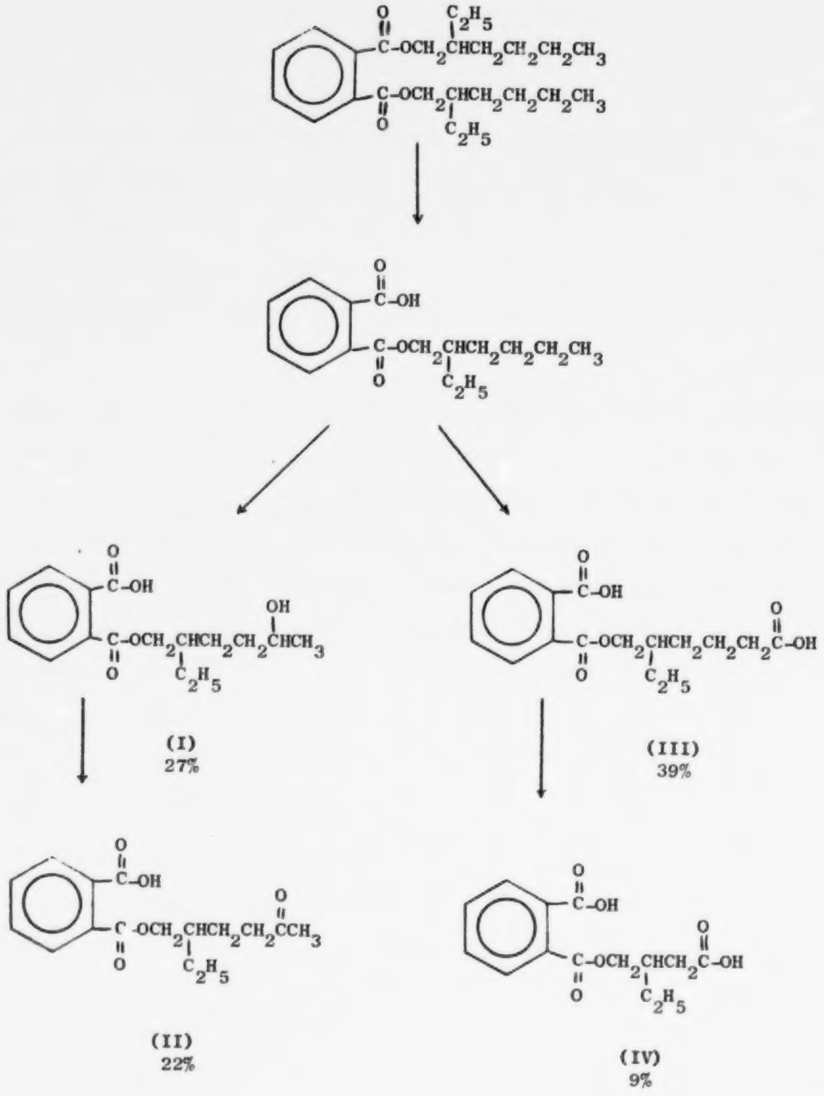


Figure 2: Metabolism of DEHP in the Rat

Source: Based on Albro, *et al.*(1973)

by gavage. The major urinary metabolites of *DMP* were monomethyl phthalate (77.5%) and phthalic acid (14.4%), as well as 8.1% unchanged *DMP*. The major metabolite of *DBP* was monobutyl phthalate (89.8%). Derivatives of this metabolite produced by ω- and (ω-1)-oxidation (as with *DEHP*) were also present in the urine at low levels (0.1-3.5%), and phthalic acid was detected at a low level (2.7%). *DOP* appeared to be metabolized in a manner very similar to *DEHP*. Although monooctyl phthalate was virtually absent from the urine (0.1%), the metabolites were all derivatives of the monoester which would be formed by ω- or (ω-1)-oxidation of the remaining octyl chain, followed by successive α- and β-oxidations.

Lake, *et al*. (1977) reported *in vitro* hydrolysis of *DMP*, *DEP*, *DBP*, *DCHP*, *DOP*, and *DEHP* to the monoesters by human intestinal preparations. In a similar study with the same compounds, Rowland, *et al*. (1977) reported that the rate of *in vitro* hydrolysis of the compounds to the monoesters in the presence of rat small intestinal contents was greater for the lower molecular weight compounds (*DMP* to *DBP*).

CRESOLS AND CRESYLIC ACID

A. Summary of Physical and Chemical Data

1. Identification and Properties of Compounds

a. Structure and Nomenclature

This class of chemicals includes the following commercially significant products: ortho-, meta-, and para-cresol, cresols (mixed), and cresylic acid. The Chemical Abstracts Registry Serial Numbers the molecular structures, the molecular formulas, and synonyms of these compounds are shown in Table I.

The exact compositions of the mixed cresols and of cresylic acid are not known. As defined by the U.S. International Trade Commission, phenolic mixtures in which 50% boils below 204°C are called cresols, and mixtures in which 50% boils above 204°C are called cresylic acids. These products are not merely mixtures of the three cresols but are much wider fractions of phenolic compounds derived from coal tar or petroleum, which also contain phenol, xylenols, and other higher-boiling phenols.

b. Chemical and Physical Properties

(1) Chemical Properties

The cresols and cresylic acid react similarly to phenol. They are mildly acidic, forming alkali-metal salts at about pH 10 which are soluble in water and can be regenerated to the cresols by treatment with mineral acids or carbon dioxide.

The cresols are readily substituted by both electrophilic and nucleophilic reagents. The substituent groups add, where possible, in the ortho- and para-positions relative to the hydroxyl groups. Although acidic, the cresols will form esters such as tricresyl phosplates with weak acids or acid chlorides.

Oxidation of the cresols yields different and generally complex products depending on the oxidizing agent used. Catalytic reduction with noble metals convert the cresols to methylcyclohexanols and/or

Table I

Structure and Nomenclature of Cresols and Cresylic Acid

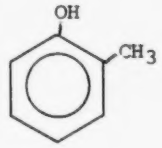
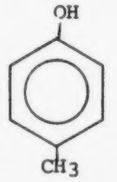
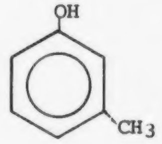
CAS Number	Name (Chem. Abstr. Name)	Structure & Molecular Formula	Synonyms
95-48-8	ortho-Cresol	 C_7H_8O	o-Cresol; 2-cresol; o-cresole; o-cresylic acid; 1-hydroxy-2-methylbenzene; o-hydroxytoluene; 2-hydroxytoluene; o-methyl-hydroxybenzene; o-methylphenol; 2-methylphenol; o-methyl-phenylol; o-oxytoluene; o-toluol; o-tolyl alcohol
106-44-5	para-Cresol	 C_7H_8O	p-Cresol; 4-cresol; p-cresole; p-cresylic acid; 1-hydroxy-4-methylbenzene; p-hydroxytoluene; 4-hydroxytoluene; p-methylhydroxybenzene; p-methylphenol; 4-methylphenol; p-methyl-phenylol; p-oxytoluene; p-toluol; p-tolyl alcohol
108-39-4	meta-Cresol	 C_7H_8O	m-Cresol; 3-cresol; m-cresole; m-cresylic acid; 1-hydroxy-3-methylbenzene; m-hydroxytoluene; 3-hydroxytoluene; m-methylhydroxybenzene; m-methylphenol; 3-methylphenol; m-methyl-phenylol; m-oxytoluene; m-toluol m-tolyl alcohol

Table I (Concluded)

CAS Number	(Chem. Abstr. Name)	Structure & Molecular Formula	Synonyms
1319-77-3	Cresols mixed	Mixture of the three isomers	Bacillol; cresoles; hydroxy-methylbenzenes; hydroxytoluenes; methyl-hydroxy-benzenes; methylphenols; methyl-phenylols; oxytoluenes; ar-toluenols; toluols; tolyl alcohols; tricresols
8006-62-0	Cresylic acid	Mixture of three isomers plus phenol, other substituted phenols, and xylenols	

methylcyclohexanones depending upon the catalyst and conditions used. Treatment of cresols with hydrogen in the vapor phase over mixed oxide catalysts generally results in conversion to toluene or benzene.

The three cresol isomers do not all possess the same degree of activity when condensed with formaldehyde to produce cresol-formaldehyde resins. The o- and p-isomers react more slowly than m-cresol , and give less highly crosslinked products (McNeil, 1965).

(2) Physical Properties

Selected physical properties of the cresols and cresylic acid, where available, are listed in Table II.

2. Known or Likely Contaminants

o-Cresol has been reported to contain the following contaminants: phenol, m-cresol, p-cresol, and 2-xylenol. m-Cresol and p-cresol probably contain the other isomers of cresol as contaminants. Mixed cresols are likely to contain other phenols and cresylic acid is reported to contain phenol, cresols, xylenols, and other higher boiling phenols. Cresols and cresylic acid derived from coal tar and petroleum may contain traces of pyridine bases and neutral oils (McNeil, 1965; Hawley, 1978).

3. Composition of Mixtures

Cresols and cresylic acid are obtained primarily as isomeric mixtures from the refining of coal tar acids and the thermal or catalytic cracking of petroleum. The initial separation of the crude acids, in both methods, yields a phenolic mixture which contains mainly cresols, phenols, and xylenols. These may be separated further to meet a wide variety of specifications and grades of either mixtures of cresols or or individual isomers. Each manufacturer produces grades of cresols according to mutually agreed upon customer specifications (McNeil, 1964).

As mentioned earlier, phenolic mixtures in which 50% of the material boils above 204°C are called cresylic acids and mixtures in which 50%

Table II

Physical Properties of Cresols and Cresylic Acid

	o-Cresol	m-Cresol	p-Cresol	Mixed Cresols	Cresylic Acid
Description	Colorless crystals	Liquid at room temperature	White crystals	solid or liquid	solid or liquid
Melting Point (°C)	30.8	10.9	35.5	11-35	--
Boiling Point (°C)	191.003	202.251	201.94	50% <204	50% >204
Density, d_4^{20}	1.0465	1.0341	1.0341	a	a
Solubility					
Water, g/100 g (°C)	1.3 (0) 4.5 (104.5)	2.7 (50.8) 4.5 (92.2)	17.0 (35) 5.4 (105)	a	a
Other	Soluble in mineral oil (2.5%), readily soluble in organic solvents, vegetable oils, diethyl ether, and ethyl alcohol	Readily soluble in organic solvents, vegetable oils, and ethyl alcohol	Miscible with organic solvents, vegetable oils, diethyl ether, and ethyl alcohol	a	a
Vapor Pressure mm Hg (25°C)	0.2453	0.1528	0.1080	a	a
Disassociation Constant (Ka)	0.63×10^{-10}	0.98×10^{-10}	0.67×10^{-10}	a	a
Lipid/Water Partition Coefficient (log P)[b]	1.95	1.95	1.95	a	a

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Source: Compiled from several sources, including McNeil (1965); Hawley (1977); Hatch & Matar (1977); Windholz (1976); and Sax (1975).

a. Similar to properties of a mixture of cresol isomers

b. In octanol (Machleid, et al., 1972; Dum & Hansch, unpublished data) boils below 204°C are called mixed cresols. The mixed cresols and cresylic acids used for the manufacture of phenolic resins are available in grades based on distillation range, minimum content of the meta- and para-isomers, and maximum content of neutral oils and pyridine bases.

One commercial grade of refined cresylic acid has been reported to have the following composition (by weight): o-cresol, 12-15%; m-cresol, 13-17%; p-cresol, 5-6%; phenol 8-9%; xylenols, 27-32%; and other phenols 27-32%.

Commercial mixed cresols contain about 20% o-cresol, 40% m-cresol, 30% p-cresol and small amounts of phenol and xylenols.

Although o-cresol can be separated from the others by fractionation of crude tar acids, the meta- and para-isomers boil at nearly the same temperature and consequently are frequently sold as mixtures. These mixtures are commercially available from coal tar and petroleum refining sources in a variety of grades. The grades are usually specified by the minimum m-cresol content (e.g., 50 to 70%), distillation range, neutral oil content (e.g., 0.25% maximum) and pyridine-base content.

The ortho-cresol appears to be the only isomer available in a relatively pure state when produced from petroleum or coal tar. Although there are no industry-wide specifications, this o-cresol is generally available in four grades: 98.5-99.5% (minimum freezing point, 30.5°C); 97.5-98.5% (freezing point, 30.0-30.49°C); 95-97.5% (freezing point, 29.0-29.99°C) and 85-95% (freezing point, 25-28.99°C). The contents of neutral and basic impurities are restricted to 0.25% and 0.1%, respectively.

The US Pharmacopeia describes a mixture of cresols for use as a reagent. The specification for this Reagent Grade cresol require that 90% distills between 195 and 205°C and that the specific gravity is 1.030-1.038.

The National Formulary (Twelfth Edition, 1965) describes a mixture of cresols, with the same specifications as the USP Reagent Grade, for use as a disinfectant. This entry was included in N.F. XIII (1970) but was not included in N.F. XIV (1975).

B. Summary of Data on Occupational and Environmental Exposure

1. Names and Locations of Producers

The cresol and cresylic acid products believed to be commercially produced at the present time are listed in Table III along with the compnies that produce them. These companies and the locations of their producing plants are listed in Table IV. Additional data on the producers of cresylic acid, including annual capacity and information on raw materials is given in Table V.

The numbers in the columns in Table III refer to the sources used to determine the commerciality of the chemicals (see footnote in Table III). The 1976 edition of Synthetic Organic Chemicals was given first priority since the minimum quantity which the International Trade Commission requires for inclusion therein is 5000 pounds (or $5000 worth) per producer. The requirements for the 1975 Synthetic Organic Chemicals and the 1977 Directory of Chemical Producres are 1000 pounds (or $1000 worth) per producers.

2. Production and Trade Statistics

The reported total U.S. production of cresols and refined cresylic acid in recent years are shown in Table VI and the reported U.S. imports are given in Table VII.

In 1964, the last year for which separate exports data were reported, U.S. exports of cresols and cresylic acid (natural and synthetic; code 512.80240) were reported to have been 10.5 million pounds. Since 1965, cresols and cresylic acid have been aggregated in the code 512.0219 (Coal tar and other cyclic intermediate acids, except phenol and isophthalic acid) with more than 100 chemicals. Industry sources estimate that about 15 million pounds of cresols and cresylic acid were exported in 1975. On January 1, 1978,

Table III

U.S. Producers of Cresols and Cresylic Acid [a,b]

Chemical	Continental Oil Co.	Fallek Chemical Co.	Ferro Corp.	Koppers Co., Inc.	The Merichem Co.	Mobil Corp.	The Sherwin-Williams Co.	Stimson Lumber Co.	United States Steel Corp.
o-Cresol*	7		$6^{c,d}$	6^{c}	6^{d}		6^{d}	7	
m-Cresol				6					
p-Cresol							6		
m, p-Cresol Mixture	7		$6^{c,d}$	6^{c}	6^{d}			6^{d}	
Mixed Cresols	6^{e}		7	6^{c}	7				
Cresylic Acid*	7	7	$6^{c,d}$	6^{c}	6^{d}	7		5^{d}	7

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* Current production volumes given in Table V

a. Numbers in columns refer to the following sources:

6= 1976 Synthetic Organic Chemicals, U.S. Production and Sales
5= 1975 Synthetic Organic Chemicals, U.S. Production and Sales
7= 1977 Directory of Chemical Producers

See discussion in text for priority of these sources.

b. See Table IV for locations of producers
c. From coal tar
d. From petroleum
e. From sources other than coal tar

Table IV

Location of U.S. Producers of Cresols and Cresylic Acid

Company	Division	Location
Continental Oil Co.	Conoco Chemicals Division Pitt - Consol Chemicals	Newark, N.J. 07105
Fallek Chemical Co.	Alabama Western Chemical Corporation, Subsidiary	Tuscaloosa, Ala. 35400
Ferro Corp.	Productol Chemical Division	Santa Fe Springs, Ca. 90670
Koppers Company, Inc.	Organic Materials Division	Follansbee, W. Va. 26037
The Merichem Co.	--	Houston, Tex. 77015
Mobil Corp.	Mobil Oil Corporation United States Division	Beaumont, Tex. 77704
The Sherwin-Williams Co.	Chemicals Group Chemicals Division	Chicago, Ill. 60628
Stimson Lumber Co.	Northwest Petrochemicals Corporation, division	Anacortes, Wash. 98221
United States Steel Corp.	USS Chemicals, division	Clairton, Pa. 15025

Table V

Capacity and Raw Materials of Cresylic Acid Producers

		Annual Capacity (Millions of Pounds)	Raw Material
Continental Oil Co. Conoco Chems. Div. Pitt-Consol Chems.	Newark, N.J.	50	Phenols and methanol
Fallek Chem. Co. Alabama Western Chem. Corp. subsid.	Tuscaloosa, Ala.	20	Petroleum
Ferro Corp. Productol Chem. Div.	Santa Fe Springs, Calif.	30	Petroleum
Koppers Co., Inc. Organic Materials Div.	Follansbee, W.Va.	5	Phenols and methanol
		30	Coal tar
The Merichem Co.	Houston, Tex.	100	Petroleum; recycles cresylate spent caustics and sulfide spent caustics
Mobil Corp. Mobil Oil Corp. United States Div.	Beaumont, Tex.	3	Petroleum
Stimson Lumber Co. Northwest Petrochem. Corp. div.	Anacortes, Wash.	30	Petroleum
United States Stel Corp. USS Chems. div.	Clairton, Pa.	20	Coal tar
	TOTAL	288	

Note: Capacity figures are for tar acids, including cresols and natural phenol, and represent ability to produce tar acids provided feedstocks are available.

Source: Directory of Chemical Producers (1977), published by SRI International

Table VI

U.S. Production of Cresols and Refined Cresylic Acid

(thousands of pounds)

Year	ortho-Cresol	meta-Cresol	para-Cresol	Cresol (meta-, para-mixture)	Total Cresols[a,b]	Refined Cresylic Acid[a]
1970	23,110	> 2	> 2	41,007	91,414	98,334
1971	22,736	> 2	> 2	39,182	87,674	69,475
1972	49,668	> 2	> 2	28,292	106,273	54,981
1973	24,741	> 1	> 1	31,377	115,436	57,524
1974	23,354	> 1	> 1	> 4	114,015	77,271
1975	20,481	> 1	> 1	> 4	93,220	44,852
1976	22,187	> 5	> 5	>25	100,221	57,107
			(thousands of kilograms)			
1970	10,492	>0.9	>0.9	18,617	41,502	44,644
1971	10,322	>0.9	>0.9	17,789	39,804	31,542
1972	22,549	>0.9	>0.9	12,845	48,248	24,961
1973	11,232	>0.45	>0.45	14,245	52,408	26,116
1974	10,603	>0.45	>0.45	> 1.8	51,763	35,081
1975	9,298	>0.45	>0.45	> 1.8	42,322	20,363
1976	10,073	>2.3	>2.3	>11.4	45,500	25,927

Source: Synthetic Organic Chemicals, US Production and Sales, Published by the US International Trade Commission

a. Includes orth-cresol, meta-cresol, para-cresol, meta-, para-cresol mixtures, and ortho, meta-, para-cresol mixtures from coal tar and petroleum sources.

b. Data for 1970-1974 include data for coke ovens and gas-retort ovens, reported to the Division of Fuels Data, U.S. Bureau of Mines. Data for 1975 and 1976 exclude production from these sources. The Bureau of Mines only reports that the combined value of "other tar derivatives" (including cresoate oil, cresols, cresylic acid, naphthalene, phenol, refined tar, and tar paint) amounted to $13.3 million in 1975 (1975 Bureau of Mines, Minerals Yearbook, Coke and Coal Chemicals Preprint, p.40)

Table VII

U.S. Imports of Cresols and Cresylic Acid

(thousands of pounds)

	Imports Through Principal U.S. Customs Districts			Total Imports	
Year	meta-Cresol	para-Cresol	Cresol (meta-, para-mixture)	Cresols[a]	Crude Cresylic Acid [b]
1970	2	2,059	5,341	7,707	7,900
1971	2	5,671	14,743	20,416	5,000
1972	82	4,970	9,083	17,702	4,200
1973	223	5,209	5,886	11,188	800
1974	311	7,505	9,917	19,720	300
1975	60	4,741	7,079	10,574	600
1976	101	4,248		4,610	300
	(thousands of kilograms)				
1970	.9	935	2,425	3,499	3591
1971	.9	2,575	6,693	9,269	2273
1972	37	2,256	4,124	8,037	1909
1973	101	2,356	2,672	5,079	364
1974	141	3,407	4,502	8,953	136
1975	27.2	2,152	3,214	4,801	273
1976	45.9	1,929		2,083	136

Source: Imports of Benzenoid Chemicals and Products, published by the US International Trade Commission; and US Imports for Consumption and General Imports, published by the US Department of Commerce.

a. Described as o-, m-, p-, and m-,p-, all having a purity of 75% minimum

b. Described as having 5% maximum boiling below 190°C and 75% boiling below 215°C the U.S. International Trade Commission established an industry code (401.09) for the reporting of exports of cresylic acid (having a boiling point of 204°C or above). Thus, data on exports should be available in the future.

3. Use Patterns

The 1976 consumption pattern for the cresols and cresylic acid has been reported to be as follows:

Use*	Percentage
Phosphate esters	20
Magnet wire	15
Antioxidants	15
Resins	15
Export	10
Cleaning compounds	6
Ore flotation	6
Miscellaneous uses	13
TOTAL	100

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*Anonymous, 1976

Commercially produced phosphate esters based on cresols and cresylic acids include tricresyl phosphate and cresyl diphenyl phosphate. Separate production data for tricresyl phosphate (which is believed to be produced from the meta-, para-cresol mixture and from cresylic acids) have not been reported since 1973 but U.S. production in 1974 is estimated to have been 56 million pounds (consuming an estimated 55 million pounds of cresols or cresylic acids). Production of cresyl diphenyl phosphate in 1976 was reported as 4.5 million pounds (consuming an estimated 1.6 million pounds of cresols). These phosphate esters are used as flame retardants with a secondary plasticizing function in polyvinyl chloride and a number of other resins (McNeil, 1965; US International Trade Commission, 1970-1976).

Cresylic acids are believed to be used as solvents for nylon and other polymers in the production of magnet wire coatings.

Antioxidants produced from cresols include 4-methyl-2,6-di-tert-butylphenol (also known as 2,6-di-tert-butyl-p-cresol, butylated hydroxytoluene, and BHT), 2,2-methylenebis(6-tert-butyl-p-cresol), and 2,2'-methylenebis-6-(1-methylcyclohexyl)-p-cresol derived from p-cresol plus 4,4'-butylidenebis(6-tert-butyl-m-cresol), 4,4'-thiobis(6-tert-butyl-m-cresol) and 1,1,3-tri(2-methyl-4-hydroxy-5-tert-butylphenyl)-butane derived from m-cresol. The first of these antioxidants, BHT, is believed to be the most important. In 1976, U.S. production of food grade BHT amounted to 8.9 million pounds and 10.9 million pounds of technical grade BHT were produced (McNeil, 1965; US International Trade Commission, 1976).

Consumption of cresols in phenol-formaldehyde type resins appears to be limited to m-cresol (for resins used in molding compositions and adhesives) and p-cresol (for oil-soluble resins) (McNeil, 1965).

Cleaning compounds are believed to include products marketed as disinfectants for home and industrial uses. Although so-called generic lysol (which is available in the United Kingdom and other countries) contains cresol and soap, the trade name Lysol(R) products sold in the U.S. do not contain cresols. No evidence was found that cresols themselves are components of commonly used cleaning formulations with the possible exception of some stock and poultry cleaners, paint removers, and products termed phenol disinfectants (Gosselin, et al., 1976).

Ore flotation agents made from cresols, or, more likely, cresylic acids include dicresylphosphorodithioic acid and its ammonium and sodium salts. These products are believed to be used as collectors for sulfide ores of metals such as copper, lead, zinc, and antimony (Anonymous, 1976b). Cresols and cresylic acid also find use in ore flotation as frothers (Fuerstenau, 1962).

Miscellaneous uses of cresols and cresylic acids include their usage as chemical intermediates for other chemicals as well as a variety of applications for the chemicals themselves.

A derivative of o-cresol, 2-chloro-4-nitro-o-cresol, is reportedly used as an intermediate in the manufacture of sulfur dyes. Another derivative, o-cresolinic acid has been reported to be used to produce some cotton and azo dyestuffs (McNeil, 1965).

Cresylic acid has been reported to be used as a metal degreasing agent but this could not be verified (McNeil, 1965).

The sulfonated derivatives of cresol formaldehyde condensates are used as synthetic tanning agents (McNeil, 1965).

A major use of o-cresol is in the manufacture of the herbicides, 2,4-dinitro-o-cresol (DNOC), and 2-methyl-4-chlorophenoxyacetic acid (MCPA). U.S. consumption of MCPA is estimated to have been 3.9 million pounds in 1975. Very small quantities of p-cresol are used as a flavoring agent in foods and in perfumes and some of its derivatives find use in this field (McNeil, 1965).

4. Occupational Standards and Workers Exposed

The U.S. Occupational Safety and Health Administration health standards for exposure to air contaminants require that an employee's exposure to cresol (all isomers) does not exceed an eight-hour time-weighted average of 5 ppm (approximately 22 mg/m^3) in the working atmosphere in any eight-hour work shift for a forty-hour work week.

Based on the 1974 National Occupational Hazard Survey (NOHS) of plants in selected industries, NIOSH has estimated the total number of workers exposed to certain chemicals in these industries. The NIOSH estimate of the number exposed to cresols is 1,913,823 people. Based on the available data, it is estimated that 32,000 people were exposed to ortho-cresol, 9,000 to meta-cresol, and 14,000 to para-cresol.

5&6. Mode of Entry and Quantities Released into the Environment

Little quantitative data was located which estimated the amounts of cresols and cresylic acid that are released into the environment.

In a recent review article, Gordon (1976) reported that no data on ambient concentrations of cresols in air were found. He concluded that the principal sources of cresol emissions to the atmosphere are the production of cresols and coke and estimated that annual U.S. emissions of cresol to the air amounted to 443 thousand pounds during cresol production (231 thousand pounds from coal tar and petroleum-derived products and 212 thousand pounds from synthesis of p-cresol) and 2,950 thousand pounds during coke production. Based on a model for a hypothetical plant producing 80 million pounds-per-year cresol, Gordon concluded that the population living in the vicinity of cresol production plants is at low risk of exposure to cresols.

This author also estimated that total annual emissions to waste water from cresol production amounted to 244 thousand pounds (127 thousand pounds from coal tar and petroleum derived products and 117 thousand pounds from synthesis of p-cresol).

No estimate was made by this author of the amount of cresols and cresylic acid released into the environment as a result of the disposal of these chemicals or products containing them.

Gordon (1976) pointed out that cresols occur in various substances to which workers and the general population are exposed. He specifically mentioned tea, fragrances, (including ylang ylang and oil of jasmine), tobacco leaves and smoke, marijuana smoke, and household disinfectants. He does not estimate the quantities released from these sources.

7. Environmental Transport

Little is known about the environmental transport of cresols, but the most recent and relevant information available from a critical literature review and laboratory studies indicates that volatilization of p-cresol is not important to its environmental fate. Smith et al. (1977) calculated (by the methods of Mackay & Wolkoff, 1973) the volatilization half-life for p-cresol from a lake to be 167 days, and estimated the Henry's law constant to be 36 torr. Using the method of Hill et al. (1976), these researchers measured the volatilization half-life of p-cresol in aqueous solution to be about 160 hours at a moderate stirring rate. The volatilization rate constants listed in the following table indicate p-cresol is not very volatile.

TABLE VIII Volatilization Rate Constants for p-Cresol

	Oxygen reaeration rate, k_v^0 (hr^{-1})	p-Cresol volatilization rate, k_v^C (hr^{-1})	Ratio k_v^C/k_v^0
Experiment 1	3.55 ± 0.24	$(3.38 \pm 0.67) \times 10^{-3}$	$(0.95 \pm 0.25) \times 10^{-3}$
Experiment 2	2.97 ± 0.21	$(4.50 \pm 0.39) \times 10^{-3}$	$(1.5 \pm 0.24) \times 10^{-3}$
Average			$(1.2 \pm .3) \times 10^{-3}$

Source: Smith, et al., 1977

These experiments noted that it was difficult to measure the volatilization because biodegradation was so rapid (see Section B.8.).

No information was found on the volatilization of the other cresol isomers or mixtures but it is probable that because their physical and chemical properties are similar to those of para-cresol, their fates are also similar to those of the para-isomer. (See Physical/Chemical properties, Table I.)

Smith, et al. (1977) have also examined the distribution of the para-isomer in water and concluded that both sorption and volatility are unimportant in the transport of the chemical. The high solubility of cresols suggested that they will remain in solution and transport will be governed by the hydrological factors in the water body (i.e., dilution, flow rates, et.).

Little is known about the sorption or transport of cresols in naturally-occurring soils. Smith, et al. (1977) examined the sorption of p-cresol on the clay, and sediments and measured a partition coefficient ($^{\text{sediment}}/\text{water}$) of 9.1 ± 6.5 on sediment from a creek in California. From their experiments, the authors concluded that p-cresol will not be significantly sorbed onto sediments. The lack of sorption and the rapid biodegradation indicate desorption from sediments will not be a source of pollution over the long term. By extrapolation on the basis on similarities in physical and chemical properties this may also be true for the other cresol isomers.

No information was found in the literature on the bioaccumulation of cresols.

8. Environmental Degradation

The major environmental degradation pathway for cresols is biodegradation by soil and water bacteria (primarily Pseudomonas sp.), although biodegradation by yeast, algae, higher plants, and mammals is also known to occur. There are a multiplicity of degradative pathways, depending on the species and particular isomer involved.

The common genus of bacteria, Pseudomonas, frequently occur in soil and water, and degrade cresols either by oxidation of the methyl group followed by ring cleavage, or by ring hydroxylation followed by ring cleavage.

Dagly and Patel (1957) have shown that degradation of p-cresol by a non-fluorescent Pseudomonas putida strain N.C.1.B.8893 is initiated by oxidation of the methyl group; p-hydroxybenzaldehyde and p-hydroxybenzoic acid are successive metabolites in the formation of the protocatechuic acid that undergoes benzene ring fission. When cresols are metabolized by certain fluorescent species of Pseudomonas, the ring-fission substrate is a catechol with an unoxidized cresylic methyl group (Dagley, et al., 1964; Ribbons, 1964). That is, p-cresol is oxidized by Pseudomonas U to 4-methyl catechol which is cleaved to form 2-hydroxy-5-methyl muconic semialdehyde (Bayly, et al., 1966; Dagley, et al., 1964). Cell extracts of Pseudomonas putida U have been reported to oxidize the semialdehyde to 4-hydroxy-2-ketovalerate (Nishizuka, et al., 1962). In a similar manner, o-cresol is oxidized to 3-methyl catechol and 2-hydroxy-6-keto-hepta-2,4-dienoic acid by Pseudomonas aeruginosa strain T1 (Ribbons, 1964; Catelani, et al. , 1968). Continued metabolism of the keto acid by this strain results in 4-hydroxy-2-keto valeric acid and acetic acid (Ribbons, 1966).

Pseudomonas putida metabolizes m-cresol to a meta-substituted catechol (presumably 4-methyl catechol) and a ring-fission product by opening of the ring between two carbons, only one of which is hydroxylated (Hopper, et al., 1975). The fission product is probably 2-hydroxy-5-methyl muconic semialdehyde.

Beyond the above studies with laboratory cultures of Pseudomonas, several experiments have shown that the naturally occurring bacteria degrade cresols in the same manner. A culture of mixed Pseudomonas sp. isolated from soil, compost, or mud from a catalytic cracking plant waste lagoon have been shown to degrade all cresol isomers (Chambers, et al., 1963). It has been estimated that there are 19 species of naturally occurring fluorescent Pseudomonas capable of degrading cresols (Cobb, et al., 1975; Olive, et al., 1976). The degradation is fairly rapid, although somewhat slower than the degradation of phenol.

Kaplin et al. (1968), in a study carried out on samples of 5 liters of river water containing 50 ml of effluent from a coking plant, observed that phenol decomposed immediately but that the cresol isomers required two days of "adaptation." Using cultures of Pseudomonas isolated from a paint-stripping room, Olive, et al. (1976) determined that optimum growth and cresol metabolism occurred at 35°C and pH 8.3; the removal rate of cresol ranged from 0.72 to 2.96 g/hour on a glass column filled with porcelain berl saddles and inoculated with a cell suspension containing 1.8 g of the isolated culture of Pseudomonas.

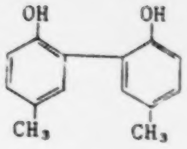
In addition to species of Pseudomonas, other bacteria are known to degrade cresols. Landa, et al. (1953) observed that an Escherichia coli strain cultivated from Moldavian water degraded p-cresol, although at a rate two to five times slower than it degraded phenol. An obligate thermophilic strain of Bacillus stearothermophilus (strain PH24), isolated from industrial sediments, was reported to grow readily at 55°C using the cresol isomers as the major carbon source (Buswell, 1976). Cell extracts prepared from these cultures catalyzed the oxidation of o-cresol to 3-methyl catechol and m-cresol and p-cresol to 4-methyl catechol. Decomposition of o-cresol by a species of Achromobacter (generally this genus occurs in soil or in fresh or salt water) has also been reported (Claus, 1964). Fourteen species belonging to the genera Achromobacter, Micrococcus, and Vibrio are known to use cresols as carbon sources (Kramer & Doetsch, 1950). But no information is available on the rate of environmental degradation of cresols by these bacteria.

Certain fungi can also degrade the cresols. Landa, et al. (1953) observed that an Oospora culture (a genus of imperfect fungi which is associated with disease of citrus trees and potatoes) degraded cresols, but more slowly than did Escherichia coli. The yeast Candida tropicalis (commonly part of the normal flora of the skin, mouth, intestinal tract, and vagina) has been found to degrade cresols only if sensitized by treatment with phenol (Nei, et al., 1973; Hashimoto, K., 1973). The metabolite from p- or m-cresol degradation by C. tropicalis phenol-adapted cells was isolated and identified as 5-formyl-2-hydroxy-4-methyl-2,4-pentadienoic acid. The same compound was obtained when 4-methyl catechol was used as a substrate. It was suggested by the authors that p- and m-cresol are hydroxylated to form 4-methyl catechol, followed by ring cleavage (Hashimoto, 1973). The oxidation of o-cresol at a slower rate was also demonstrated. The yeast Trichosporon cutaneum can also use the cresols as a carbon source (Neujahr and Varga, 1970).

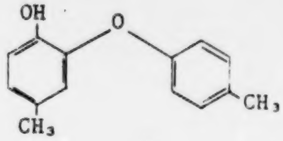
Algae (Nitella, Chara fragilis and Dodegonium) and higher aquatic plants (Elodea canadenis and Myriophyllum) degrade p-cresol (Timofeeva, 1975). Under test conditions, p-cresol, at an initial concentration of 10^{-3}M, disappeared entirely from the solution within 15-20 days. p-Cresol was degraded faster than phenol in this test system, but more slowly than pyrocatechol or hydroquinone.

The importance of the rapid biodegradation of cresols in the environment has been demonstrated by the experiments of Smith, et al. (1977) with p-cresol and mixed microbial cultures obtained from environmental samples. Enrichment biodegrading systems were obtained with water samples from several Northern California locations (including Coyote Creek, a pond near Searsville Lake, aeration effluents from the Palo Alto and South San Francisco sewage plants, aeration effluent from a Shell Oil refinery wastewater treatment plant, and Lake Tahoe). There were inductive (or lag) periods before p-cresol biodegradation began. For example, in eutrophic pond water no significant biodegradation occurred until 5.5 and 6 hours for concentrations of 3 or 10 μg/ml, respectively; degradation was complete at 7 and 8.5 hours, respectively. For the effluent from the Palo Alto sewage plant, total degradation at the 3 and 10 μg/ml p-cresol levels occurred at <4 and 6 hours, respectively. In one experiment with pond water and extreme levels of 100, 300, and 1000 μg/ml p-cresol, the respective degradations and times were 100% at <24 hours, 100% at approximately 32 hours, and 30% at 72 hours. Apparently, the highest concentration inhibited or killed many microorganisms. The cultures from Lake Tahoe water, and Lake Tahoe water mixed with sediment and allowed to settle, showed total decomposition of 10 μg/ml p-cresol in <144 and <96 hours, respectively. On microscopic examination and in a plating-out study of the Lake Tahoe cultures it was obvious that many types of microorganisms were present. It is not known how many of these were primary utilizers of p-cresol, or secondary utilizers that grew on metabolites, or how many grew on excretion products associated with living or dying p-cresol metabolizers. These mixed cultures are, however, more representative of conditions in nature and probably include many of the microorganisms previously discussed.

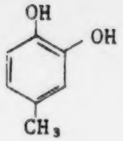
In addition to biodegradation, photolytic degradation of cresols may occur in the environment. Direct photolysis of p-cresol in water at 254 nm gave 2,2'-dihydroxy-4,4'-dimethylbiphenyl (I), 2-hydroxy-3,4'-dimethyldiphenylether (II), and 4-methylcatechol (III) (Miller, et al., 1977).



I



II

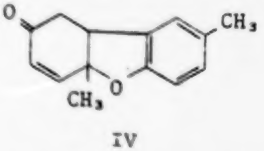


III

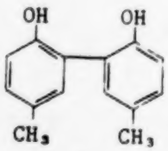
Dye-senitized (methylene blue) photooxidation of mixed cresols in organic wastes has also been reported, although the oxidation products have not been identified (Sargent and Sanks, 1974); this is probably not environmentally relevant because of the reaction conditions.

Based on their calculations and laboratory studies, Smith, et al. (1977) suggested that photolysis is an important environmental degradation pathway for p-cresol, and probably for the other cresol isomers. The half-life for direct photolysis of p-cresol in sunlight as a function of the time of year was calculated by the procedure of Zepp and Cline (1977) using the quantum yield of 0.079 and the measured UV absorption spectrum of p-cresol; these data are plotted in Figure 1. It should be noted that the experimentally measured half-life for the solar photolysis of p-cresol is about 35 days (see Table IX, footnote e).

Smith, et al. (1977) have also shown that the presence of humic acid in solution accelerates the photolysis of p-cresol by factors of 2-12 compared to photolysis in pure water. It was postulated that this acceleration may arise from a sensitized photolysis in which humic acid serves to transfer excitation energy to p-cresol; humic acid could act as a photoinitiator (a triplet diradical, for example) that initiates a radical oxidation process. Reaction products from photooxidation of p-cresol in the presence of 4,4'-azo bis(4-cyanovaleric acid) were Pummerer's ketone (IV) and 2,2'-dihydroxy-4,4'-dimethylbiphenyl (I); these were identified by comparing retention time with those samples prepared by literature procedures (Haynes, et al., 1956).



IV



I

These two products accounted for only about 25% of the reacted p-cresol, and after an initial photoperiod, the biphenyl began to decrease with longer irradiation.

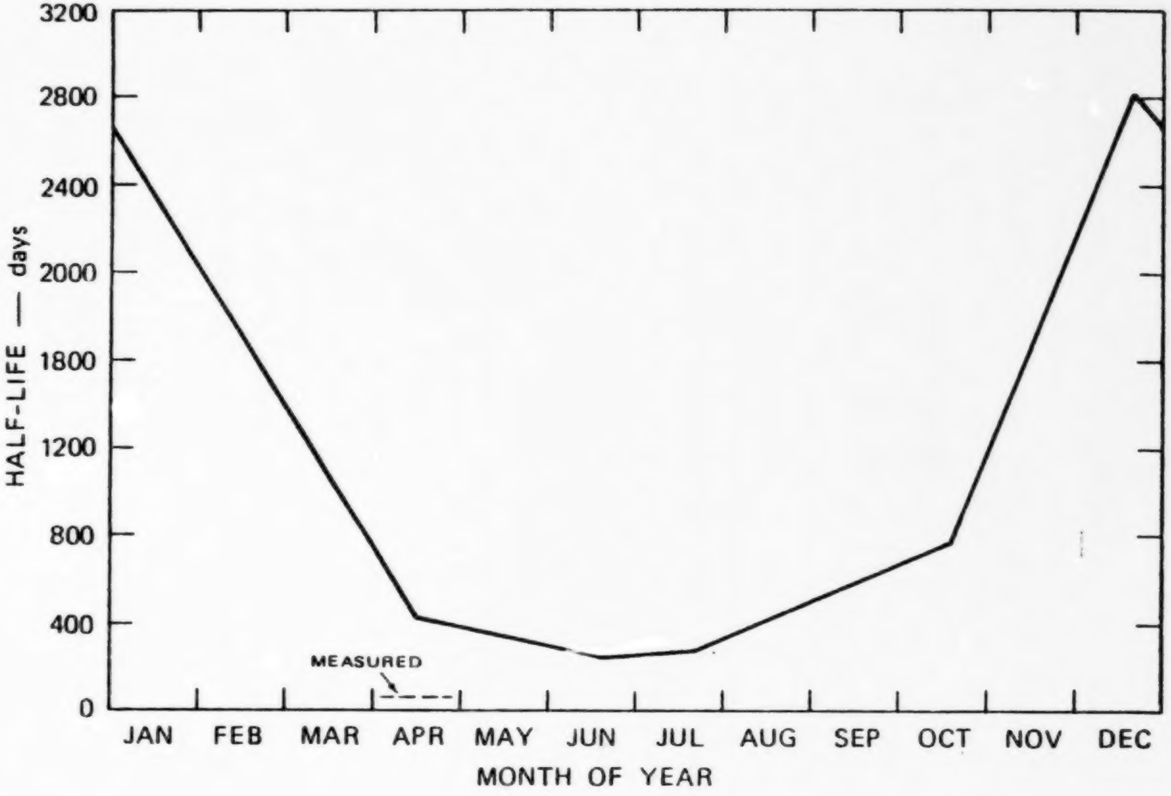


FIGURE 1 ANNUAL VARIATION OF PHOTOLYSIS HALF-LIFE FOR p-CRESOL

Source: Smith, et al., 1977

TABLE IX Rate Constants for Photolysis of 1.0 μg ml^{-1} p-Cresol[a]

Irradiation source	Solution	Extent of reaction (%)	Rate constant $k_p \times 10^{-6}$ sec^{-1}	Ratio of k_p with humic acid to that in pure water
Solar, in April	Pure water	32	0.68 ± 0.12[b,c,d,e]	12
	Pure water with 9.5 μg ml^{-1} humic acid	93	8.0 ± 0.2[d,f]	

[a] 1.0 μg ml^{-1} p-cresol in water= 9.2 10^{-6} M.
[b] Standard deviation.
[c] Quantum yield for p-cresol disappearance was 0.079.
[d] Calculated assuming 12 hours of sunlight per day; weather was mostly overcast during the two-week reaction period. To obtain average ratio constant for full calendar day (24 hours), divide rate constant by three.
[e] Half-life of 35 days.
[f] Half-life of 3.0 days.

Source: Smith, et al., 1977

Although no model ecosystem studies were found for o- or m-cresol, Smith, et al. (1977) assessed the environmental fate of p-cresol using computer calculations for a one-compartment model (water), following an acute discharge (see Table X), and for nine compartments during chronic discharge to each of four types of water bodies (see Table XI).

TABLE X Transformation and Transport of p-Cresol Predicted by the Compartment Model

Process	River	Eutrophic pond	Eutrophic lake	Oligotrophic lake
Photolysis, half-life (hr)[a]	4,800	> 10,000	> 10,000	2,400
Biotransformation, half-life (hr)	12	12	12	> 10,000
Half-life for all processes except dilution (hr)	12	12	12	2,400
Half-life for all processes including dilution	0.55	12	12	2,400

[a] Estimates are the average photolysis rates on a summer day at 40° latitude. Photolysis rates in midwinter are at least three times slower.

Source: Smith, et al., 1977

TABLE XI

DISTRIBUTION OF p-CRESOL IN VARIOUS AQUATIC SYSTEMS AT STEADY STATE
(input concentrations of 1 $\mu g\ ml^{-1}$ p-cresol)

	Pond		River		Eutrophic lake		Oligotrophic lake	
	Mass (kg)	Conc. ($\mu g\ g^{-1}$)	Mass (kg)	Conc. ($\mu g\ g^{-1}$)	Mass (kg)	Conc. ($\mu g\ g^{-1}$)	Mass (kg)	Conc. ($\mu g\ g^{-1}$)
Compartment 1 (surface water)								
Solution	3.40×10^{-1}	1.70×10^{-2}	2.94×10^{4}	9.80×10^{-1}	9.44	3.77×10^{-2}	5.32×10	2.20×10^{-1}
Suspended solids	9.55×10^{-4}	1.70×10^{-1}	2.94×10^{-1}	9.80	4.72×10^{-4}	3.77×10^{-1}	2.66×10^{-2}	2.20
Compartment 2 (surface water)								
Solution	--	--	2.89×10^{4}	9.66×10^{-1}	6.02	2.40×10^{-3}	3.55×10^{2}	1.28×10^{-1}
Suspended solids	--	--	2.89×10^{-1}	9.66	3.01×10^{-4}	2.40×10^{-2}	1.60×10^{-1}	1.28
Compartment 3 (surface water)								
Solution	--	--	2.85×10^{4}	9.50×10^{-1}	2.49×10^{-1}	9.99×10^{-5}	1.00×10	1.20×10^{-1}
Suspended solids	--	--	2.85×10^{-1}	9.50	1.24×10^{-5}	9.99×10^{-4}	1.50×10^{-4}	1.20
Compartment 5 (bottom water)								
Solution	--	--	--	--	7.22×10^{-2}	2.89×10^{-5}	5.25×10	2.10×10^{-2}
Suspended solids	--	--	--	--	3.61×15^{-5}	2.89×10^{-4}	2.62×10^{-2}	2.10×10^{-1}
Compartments 7-9 (sediment)[a]								
Solution	4.25×10^{-2}	1.70×10^{-2}	2.41	9.65×10^{-1}	8.75×10^{-4}	9.58×10^{-3}	8.29×10^{-1}	9.48×10^{-4}
Solids	1.14×10^{-1}	1.70×10^{-1}	1.95×10^{4}	9.65	1.30	9.58×10^{-2}	1.29×10	9.48×10^{-1}

[a] The amounts given for solid and solution phases in the sediment compartments are estimated from the sorption partition coefficient for suspended solids and may be overestimated because it was assumed that biodegradation of sorbed material does not occur.

Source: Smith, et al., 1977

From these results, the authors concluded that biodegradation is the dominant transformation pathway in eutrophic waters, but it is four times slower than photolysis in oligotrophic waters. Dilution was considered important only in relation to biotransformation in rivers, and sorption and volatilization were considered unimportant in all waters.

The nine-compartment environmental exposure model predicted (using the half-lives predicted from the one-compartment model) the following steady-state concentrations of p-cresol in solution, suspended solids, and sediments near point sources in the presence of a discharge of 1 ml^{-1} (1 ppm) p-cresol:

	Half-life (hr)	Solution (ug ml^{-1})	Suspended solids (ug g^{-1})	Sediments (ug g^{-1})
River	0.55	0.980	9.80	9.65
Pond	12	0.017	0.17	0.17
Eutrophic lake	12	0.037	0.37	0.10
Oligotrophic lake	2400	0.0221	2.20	0.94

Source: Smith, *et al.*, 1977

The half-life for p-cresol in the river is small in comparison to the half-lives in other water bodies due to the higher flow rate used in the river. The higher concentrations for the river are due to the larger amount of p-cresol needed to achieve the initial concentration in the river simulation, with the rapid flow removing p-cresol from the river segment before biodegradation occurs. The half-lives of p-cresol predicted in these studies suggested to the authors that p-cresol is not persistent, "as the term is usually applied with respect to pesticides."

C. Biological Effects

1. Ecological Hazards

a. Toxicity to Wildlife

(1) Acute Toxicity

The cresol isomers are known to be directly toxic to fish, amphibians, and aquatic invertebrates; they also have a high demand which results in oxygen depletion of water and produces undesirable flavors in edible fish. Of the three isomers, the least toxic is m-cresol. Reports for the relative toxicity of o- and p-cresol are inconsistent (Mitrovic, et. al., 1973). Data on the acute toxicity of the cresol isomers and phenol were given by Albersmayer and Erichsen (1959) for several species over a range of temperatures of 13-19°C, as follows:

Approximate 24-hour LC_{50} (mg/l)

Phenols	Crucian carp	Roach	Tench	"Trout" embryos
Phenol	25	15	17	5
o-cresol	30	16	15	2
m-cresol	25	23	21	7
p-cresol	21	17	16	4

Source: Albersmayer & Erichsen (1959)

Pickering and Henderson (1966) reported the 96-hour LC_{50} of o-cresol for goldfish as 17-31 mg/l at 25°C. The 96-hour LC_{50} of o-cresol channel catfish was reported as 66.8 mg/l (Clemens and Snad, 1959). For rainbow trout, the 96-hour LC_{50} at 10°C was reported to be 3.2 to 5.6 mg/l for cresylic acid (Webb, et al., 1976). Cresylic acid has also been reported to be acutely toxic to Pacific salmon (chinook, silver, and pink species) over a concentration range of 3.12 to 6.98 mg/l during a three-day exposure in both fresh and salt water (Hawley, 1972).

The isomers of cresol incapacitate fish and fish may tend to avoid localized concentrations of the chemicals. p-Cresol is the most active of the three isomers in inducing total incapacitation of trout (Howland, 1969). Bucksteeg, et al. (1955) found that the threshold concentration for loss of coordinated movement in perch was 10 mg/l. Minnows have been reported to avoid 400 mg/l of p- and o-cresol but not lower concentrations (Jones, 1951).

The cresol isomers are also toxic to amphibians. Both m-cresol and p-cresol were lethal to frogs bu subcutaneous injection with dosages of 250 mg/kg and 150 mg/kg, respectively (Spector, 1955). The lowest lethal subcutaneous doses in the frog for the para- ortho-, and meta-isomers have been reported to be 150, 200, and 250 mg/kg respectively (Anonymous,, 1935).

The cresols are also toxic in laboratory studies to non-target invertebrates. In the fresh water crustacean Daphnia sp., 100% mortality occurs within 72 hours at a cresylic acid concentration of 0.1 mg/l (Hawley, 1972). Ellis (1937) has reported a lethal concentration to D. magna of a mixture of cresols to be 0.01 mg/l.

Studies reviewed by Mitrovic et al. (1976) indicate that, as in fish, m-cresol is the least toxic of the isomers to Daphinia sp. and p-cresol, the most toxic isomer (Bringmann and Kuhn, 1959a,b; Albersmayer & Erichsen, 1959). The minute aquatic crustacean Cyclops strenuus and the ostracod Pionocyprus vidua are also sensitive to cresols but no data on these studies are available (Albersmayer & Erichsen, 1959).

Emery (1970) determined that for Gammarus fasciatus and Asellus militaris (species of benthic crustaceans) concentrations below 0.525-0.70 mg cresols/l water were not acutely toxic. Exposure periods of 48 hours revealed that adult asellids were about twice as tolerant to cresols (mean TL_m48 65.1 mg/l) as adult gammarids (mean TL_m48 31.1 mg/l), and immature asellids were about four times as tolerant (mean TL_m48 33.3 mg/l) as immature gammarids (mean TL_m48 8.6 mg/l). Cresols are also known to be effective nematocides for soil incorporation (Establissements, 1972, 1974).

An overall aquatic toxicity rating of 10^{-1} ppm has been assigned to cresol (Christensen, 1977). This figure is derived from a bioassay conducted under static or continuous flow conditions with a variety of organisms (e.g., finfish, shrimp). Using a system of ranking outlined in Appendix A (an excerpt from Christensen, 1977), the above value can be described as highly toxic.

(2) Reproductive System Effects

No information was found on the reproductive effects of cresols.

b. Toxicity to Plants

There is some evidence that cresols can be toxic to plants. Mixed cresols have been reported to be toxic to green algae (Scenedesmus quadricauda) in a cell multiplication inhibition test, but the data were not available (Bringmann and Kuehn, 1977).

o-Cresol has been reported to be toxic to the algae Nitella sp. (Stom and Beim, 1976). At 1/32 saturation, o-cresol stopped the movement of protoplasm within 15 minutes.

Chlorosis in Lemna minor (common duckweed) is also known to be produced by o-cresol (Blackman, et al., 1955).

One study suggested o-cresol affects the reproductive process of germination by effectively breaking dormancy for barnyard grass (Echinochloa crusgalli var oryzicola). The meta- and para-isomers were ineffective (Shimizu, et al., 1972).

c. Toxicity to Microorganisms

The cresol isomers are known germicides (Berry, 1951; Khoroshavin, et al., 1971; Kaye & Proudfoot, 1971; Bean & Dempsey, 1971) capable of damaging non-pathogenic microorganisms in the environment, although, as noted in Environmental Degradation (Section B.8.) they can also serve as the carbon source for a variety of organisms. The meta-isomer is the most active against most common bacteria, especially the acid-fast bacteria (Gurney, 1972). The antibacterial activity of all the isomers is considerably decreased in the presence of soaps (as in generic lysol which is 50% solution of mixed cresols in soap) (Gosselin, et al., 1976).

m-Cresol at a concentration of 1,000 μg/ml inhibited the growth of Escherichia coli about 50% with no effect on cell size (Loveless, et al., 1954). Mixed cresols have been reported to be toxic to Pseudomonas putida in a cell multiplication inhibition test, but no data are available (Bringmann and Kuehn, 1977).

All the cresol isomers are also toxic to the ciliates Paramecium caudatum (Halsband and Halsband, 1954) and Microregma heterostoma (Bringmann and Kuehn, 1959).

Ortho-Cresol has been reported to reduce the rate of radial spread of the mycelium of the fungi Trichoderma viride (Blackman, et al., 1955). Cresols have been reported to be used as fungicides (Chakravarty and Baruah, 1970; Takahashi, 1972).

Cresols can also be toxic to viruses. Fixed rabies virus was completely inactivated in vitro by a 0.6% solution of p-cresol (Spicher and Timm, 1973). Cresols have also bee reported to kill AHC entrovirus but not Poliovirus, Coxsackie virus B-5, or Echo virus-7 (Watanabe, et al., 1975).

2. Effects Related to Human Health Hazards

a. Carcinogenicity

(1) Animal Data

No adequate tests have been reported demonstrating that any of the cresols or cresylic acid are carcinogens. Each of the three isomers, o-cresol, m-cresol, and p-cresol, have been found active as mouse skin tumor promoters (Boutwell, 1967). In these experiments, twice weekly applications of a 10% solution of the cresol in benzene were delivered to the skin of mice, beginning one week after initiation by a single topical application of 75 µg of 7,12-dimethylbenz(a)anthracene (DMBA). By 24 weeks after initiation, the incidence of skin papillomas approached 100% for each of the three isomers of cresol. For mice receiving either a single application of DMBA alone, twice weekly applications of only a 10% solution of the cresol in benzene without prior DMBA treatment, or DMBA followed by twice weekly applications of benzene only, the incidence of skin tumors was insignificant.

As part of a study of the tumor-promoting activity of subfractions of cigarette smoke condensate, an acetone solution of a synthetic distillate of known composition containing 0.204% phenol, 0.037% o-cresol, 0.035% m-cresol, 0.070% p-cresol, 0.017% 2,4-xylenol, 0.028% 3,5-xylenol, and 0.027% guaiacol was tested on mouse skin and compared to the activity of the cigarette smoke condensate (Bock, et al., 1971). The mice were initiated with a single topical application of 125 µg DMBA and, beginning three weeks later, were painted five times a week with 0.25 ml of the synthetic distillate solution. After 56 weeks of testing, skin tumors were observed in 7 of 35 survivors. No skin tumors were observed in 25 surviving controls that received DMBA followed by acetone only. In a second experiment as part of the same study, an acetone solution containing 0.231% phenol, 0.055% o-cresol, 0.045% m-cresol, 0.090% p-cresol, 0.026% 2,4-xylenol, 0.052% 3,5-xylenol, and 0.042% guaiacol was tested similarly. The incidence of skin tumors in this experiment was not signficantly different from pooled negative controls painted with DMBA and acetone only.

(2) Human Data

There have been no reports of a direct association between human cancer and chronic exposure to cresols. Cresylic acid is obtained from coal tar which is a recognized cancer hazard in humans (Hueper and Conway, 1964). Similarly, creosote (including both wood creosote and coal creosote), a mixture containing phenols and cresols, including 2-methoxy-p-cresol, and aromatic hydrocarbons, is a recognized carcinogen in humans (Hueper and Conway, 1964).

A clinical observation has been made of two patients with multifocal transitional cell carcinoma of the bladder (Garrett, 1975). Both patients had chronic exposure to cresol and creosote but details of their exposure to other chemicals or smoking habits were not revealed.

One study has been reported of the health hazards associated with coal hydrogenation processes in which the potential exists for the environmental discharge of considerable quantities of hazardous materials including cresols (Wadden, 1976). In this study of a group of workers at a coal liquefaction plant, skin cancer was found in 10 out of 359 workers examined over a five-year period. This incidence was considered 16 to 37 times the incidence of skin cancer expected in the chemical industry. Analysis of the liquids produced in this plant revealed a number of materials found to be carcinogenic in laboratory animals. High levels of benzo(a)pyrene (as much as 18,000 μg/1000 m^3), a recognized carcinogen, were also identified by air measurements in working areas. The specific presence of cresylic acid or any of the three isomeric cresols was not noted.

b. Mutagenicity

There were no mutagenicity data for cresols reported in the literature (EMIC, 1978) but there are two reports indicating that they may be capable of producing genetic damage. Chromosome fragments were seen in onion roots (*Allium cepa*) treated with the various cresol isomers (concentrations 0.1 to 0.00001 moles/liter for 4-24 hours (Levan and Tjio, 1948;

c. Teratogenicity

No information was found on the teratogenicity of cresols.

d. Systemic Toxicity

(1) Human Data

The toxicity of the cresols to humans is very similar to that of phenol (Gosselin, *et al*., 1976; Hamilton and Hardy, 1949; Deichmann and Keplinger, 1963). In the older literature it was common to group cases of phenol, cresol, and cresylic acid poisoning together (Bruce, *et al*., Isaacs, 1922; Koster, 1943). It is now believed that the toxicity of mixed cresols and the meta isomer are somewhat less than that of phenol, while o-cresol is more toxic than m-cresol and p-cresol is the most toxic of the isomers (Fairhall, 1957).

Cresols are potent primary corrosive irritants (Gafafer, 1964; Deichmann and Keplinger, 1963), and there have been several reports of severe systemic damage produced by cresol-containing substances following acute exposures by inhalation, skin absorption, or ingestion.

In general, the systemic damage produced by the cresols in humans arises primarily from effects on the central nervous system; this damage can include muscular weakness, gastrointestinal distress, severe depression, convulsions, respiratory distress, collapse, and death. Also it is not uncommon to see kidney, liver, pancreas, heart, and spleen damage, with albuminuria and hematuria (Deichmann and Keplinger, 1963; Plunkett, 1976).

There have been reports of systemic damage resulting from acute dermal or inhalational exposure to cresols. Cason (1959) reported the case of a 47-year old man who fell into a vat of "ardox" (a cresylic acid derivative). Although he was quickly removed and washed thoroughly under a shower, six hours later he was found to have apparently superficial burns over 15% of his lower body. Thirty-six hours after the accident anuria developed indicating toxic amounts of cresylic acid had been absorbed. Apart from renal insufficiency, he remained satisfactory until the seventh day when he developed respiratory distress. On the tenth day he became unconscious and developed congestive heart failure and died within 18 hours of becoming comatose. Green (1975) reported a similar case of fatal cresol poisoning from skin absorption of the cresols in Wright's Coal Tar Vaporizer (90% cresols in water). In the report, a 12-month old boy was exposed five minutes to about 20 ml of this fluid poured in his head. The boy's mother washed the fluid off with soap and water and took the boy to the hospital within ten minutes because he was "blue in the face." On admission, the boy was deeply unconscious, shocked, and cyanosed. He died in a coma four hours later. The autopsy report revealed burns on 7% of the body, but not on the lips or tongue, and there was no evidence of inhalation. Histology showed early acute kidney necrosis, extensive centrolobular and midzonal liver necrosis, and edema in the brain. In another report, a six-year-old child died after being contaminated (45% of his body surface) with undiluted generic lysol (Ferry, 1965). Histologic examination of the kidney suggested a direct nephrotoxic action in the proximal tubule. Absorption of cresols through the mucous membranes of the vagina resulted in the death of a woman within six days following use of lysol as a douche. The death was the result of pulmonary edema and renal tubular necrosis (Finzer, 1961).

There have been a number of reports on acute poisoning from ingestion of products containing the cresol isomers. Bruce, _et al_. (1976) have reported two cases of fatal poisoning from the ingestion of unknown amounts of the popular disinfectant lysol (a mixture of cresols and soap). In both cases there was brown discoloration of the face and mouth and there was extensive necrosis of the esophageal mucosa. The most striking pathological changes were in the liver and renal cortex where there were large accumulations of lipofuscin. Fisher (1955) reported on an adult male who had ingested one half pint of generic lysol. The initial signs of poisoning were a deep coma punctuated by periods of restlessness. There was pharyngeal edema, jaundice with elevated serum bilirubin, and a low platelet count, but the man eventually recovered. Two Chinese females who ingested 100 ml and 250 ml of lysol (containing 50% cresols) suffered coma, methemoglobinemia, Heinz bodies and evidence of massive intravascular hemolysis as reported by Chan, _et al_. (1971). The patient ingesting the larger dose died. Simpson (1932) reported the case of a male who ingested about 75 ml of a 50% mixed cresol ("tricresol") solution. About five to eight hours following ingestion, the patient died. The _post mortem_ examination revealed acute necrosis of the pancreas and gastric mucosa.

Limited reports from industrial situations suggest that systemic damage may also occur after chronic exposure to cresols. Workers engaged in the manufacture of enamel-coated wire and exposed to cresol vapor and heat were reported to have increased heart rates but no "severe ill effects" (Yamaguchi, 1970). Workers engaged in the production of triaryl phosphates and exposed to cresols as well as to phenol, and to tricresyl, triphenyl, and trixylyl phosphates, showed some systemic toxicity. The first stage of toxicity (which in some cases, developed after 2-3 years) was characterized by a perivascular form of polyneuritis. Often this was accompanied by decreasing activity of plasma cholinesterase and chronic gastritis. The second stage showed toxic encephalopathy, hypophthalamic syndrome, and polyneuritis (Aizenshadt, 1975).

Very early reports of industrial cresol poisoning cited liver and kidney damage, and secondary lesions of the heart and brain as the most

TABLE XII

Acute Toxicity of Cresols in Experimental Animals

CHEMICAL	ROUTE	LETHAL DOSE	SPECIES	REFERENCE
p-Cresol	Oral	LD50: 207 mg/kg	Rat	Industrial Bio Test Laboratories
		LD50: 1800 mg/kg	Rat	Deichmann & Witherup, 1944
		LD50: 1460 mg/kg	Rat	Uzhdavini, et al., 1974
		LD50: 344 mg/kg	Mouse	Uzhdavini, et al., 1974
		LD10: 620 mg/kg	Rabbit	Deichmann & Witherup, 1944
	Dermal	LD50: 750 mg/kg	Rat	Uzhdavini, et al., 1976
		LD50: 301 mg/kg	Rabbit	Industrial Bio Test Laboratories
		LD50: 3600 mg/kg	Rabbit	Denine, 1973
	Subcutaneous	LD_{10}: 150 mg/kg	Mouse	Anon., 1935
		LD_{10}: 80 mg/kg	Cat	Deichmann & Witherup, 1944
		LD_{10}: 300 mg/kg	Rabbit	Anon., 1935
	Intraperitoneal	LD_{10}: 100 mg/kg	Guinea pig	Anon., 1895
	Intravenous	LD_{10}: 180 mg/kg	Rabbit	Deichmann & Witherup, 1944
o-Cresol	Oral	LD50: 121 mg/kg	Rat	Industrial Bio Test Laboratories
		LD50: 1350 mg/kg	Rat	Deichman & Witherup, 1944
		LD50: 1470 mg/kg	Rat	Uzhdavini, et al., 1974
		LD50: 344 mg/kg	Mouse	Uzhdavini, et al., 1974
		LD10: 940 mg/kg	Rabbit	Deichmann & Witherup, 1944
	Dermal	LD50: 620 mg/kg	Rat	Uzhdavini, et al., 1976
		LD50: 1380 mg/kg	Rabbit	Industrial Bio Test Laboratories
	Subcutaneous	LD_{10}: 410 mg/kg	Mouse	Anon., 1909
		LD_{10}: 55 mg/kg	Cat	Deichmann & Witherup, 1944
		LD_{10}: 450 mg/kg	Rabbit	Anon., 1935
	Intraperitoneal	LD_{10}: 360 mg/kg	Guinea pig	Anon., 1935
	Intravenous	LD_{10}: 180 mg/kg	Rabbit	Deichmann & Witherup, 1944
m-Cresol	Oral	LD50: 242 mg/kg	Rat	Industrial Bio Test Laboratories
		LD50: 2020 mg/kg	Rat	Deichmann & Witherup, 1944
		LD50: 2010 mg/kg	Rat	Uzhdavini, et al., 1974
		LD50: 828 mg/kg	Mouse	Uzhdavini, et al., 1974
		LD_{10}: 1400 mg/kg	Rabbit	Deichmann & Witherup, 1944

Table XII (Cont'd)
Acute Toxicity of Cresols in Experimental Animals

	ROUTE	LETHAL DOSE	SPECIES	REFERENCES
	Dermal	LD50: 1100 mg/kg	Rat	Uzhdavini, et al., 1976
		LD50: 2050 mg/kg	Rabbit	Industrial Bio Test Laboratories
	Subcutaneous	LD_{10}: 450 mg/kg	Mouse	Anon., 1935
		LD_{10}: 180 mg/kg	Cat	Deichmann & Witherup, 1944
		LD_{10}: 500 mg/kg	Rabbit	Anon., 1935
	Intraperitoneal	LD_{10}: 100 mg/kg	Guinea pig	Anon., 1935
	Intravenous	LD_{10}: 280 mg/kg	Rabbit	Deichmann & Witherup, 1944
Mixed Cresols	Oral	LD50: 1454 mg/kg	Rat	NTIS PB225-283
		LD50: 861 mg/kg	Mouse	NTIS PB225-283

common manifestations of toxicity (International Labor Office, 1930; Duvoir, et al., 1938), but detailed analyses of these cases are not available.

(2) Animal Data

The toxicity of cresols is very similar to that of phenol in experimental animals on both acute and chronic exposure (Deichmann and Keplinger, 1963). As in humans, acute exposures by all routes of absorption may cause central nervous system depression, muscular weakness, gastroenteric disturbances, convulsions, and death. The acute toxicity of the cresols is summarized in Table XII.

The pathological changes induced by exposure to cresols include irritation, hemorrhages, destruction of the gastrointestinal lining (following oral administration), kidney tubule damage, nodular pneumonia, and liver damage (Deichmann and Keplinger, 1963 ; Plunkett, 1976).

Deichmann and Witherup (1944) have reported the acute oral toxicity of the cresols in rabbits and rats. When administered orally to rats in the 10% solutions in olive oil, o-cresol was the most toxic, and was followed by p-cresol, and m-cresol (Table XII). When given orally to rabbits in the form of 20% aqueous emulsions, the most toxic were p- and o-cresol; m-cresol was the least toxic. Signs and symptons of poisoning in these animals included weakness and collapse, convulsions, and coma. On the whole, the convulsions were less severe than those produced by phenol, but the cresols resulted in deeper coma. Campbell (1941) reported that "the higher-boiling petroleum cresylic materials were less toxic when ingested by white mice than the low-boiling cresylic materials."

The cresols are very corrosive and their immediate effect on skin is frequently severe burning; however, toxic amounts have been shown to be absorbed through the skin of rats (Uzhdavini and Gilev, 1976), mice (Uzhdavini, et al., 1974), and rabbits (Industrial Bio-Test Laboratories) (Table XII). Rats poisoned by dermal exposure showed hemorrhagic, dystrophic changes in the liver, kidneys, and myocardium (Uzhdavini and Gilev, 1976).

Several studies have shown that acute exposures to cresols by inhalation can result in severe systemic damage. Uzhdavini, et al. (1972) observed irritation of the mucous membranes, convulsions, and hematuria in mice given a single exposure (for an unspecified time) to a mixture of o-cresol vapor and aerosol (amounts not given). Histological examination showed lung, liver (including centrolobular necrosis), and kidney damage in mice that survived the acute poisoning. Similarly, Uzhdavini, et al. (1974) observed that all the cresol isomers produced convulsions in mice acutely exposed to vapors and aerosol (unspecified amounts). It should be noted, according to the authors, that the airborne cresol also precipitates on the skin of the animals and is absorbed through the skin. Pereima (1977) reported that p-cresol was the most toxic isomer when inhaled by rats and that m-cresol was the least toxic (no data were available).

Experiments in which animals were exposed by parenteral routes have shown that o-cresol is the most toxic isomer following acute exposures and m-cresol is the least toxic (Table XII). Deichmann and Witherup (1944) injected cats with a single subcutaneous dose of the cresols as 10% solutions in olive oil with the following results (one animal was used at each dose):

DOSE	o-CRESOL	m-CRESOL	p-CRESOL
gm./kg.	*hours till death*		
0.024	survived		
0.036	survived		survived
0.055	60		survived
0.080	60	survived	120
0.12	22	survived	84
0.18	8.5	27	21
0.28	3	4	4.5
0.42		12	10
0.62	7	7	8
0.94	4	5.5	7

Source: Deichmann & Witherup, 1944

When single intravenous doses (10.5% aqueous solutions) were given to rabbits by these same investigators, a similar relative toxicity was observed:

DOSE	o-CRESOL	m-CRESOL	p-CRESOL
gm./kg.	*hours till death*		
0.08	survived		survived
0.12	survived	survived	survived
0.18	8	survived	15
0.28	10	15	10
0.42		7	

Source: Deichmann & Witherup, 1944

There is only limited information on the chronic toxicity of cresols in experimental animals (also see Carcinogenicity Section C.2.a). In a Subchronic study, Uzhdavini, et al. (1972) exposed mice two hours per day, six days per week, for one month to o-cresol vapor and aerosol concentrations fluctuating from 26 to 76 mg/m^3, and averaging 50 mg/m^3. After 18-20 days, the ends of the tails of some of the mice had mummified and fallen off. At the end of this experiment, microscopic examination of the central nervous system showed plethora and dystrophic changes of the nerve cells and glial elements. Other pathological changes included: respiratory tract edema, lung hemorrhages, catarrhal bronchitis, dystrophic changes in the myocardium, and "protein dystrophy" in the liver and kidneys. Rats and guinea pigs were exposed to o-cresol vapor (two months, six hours per day, five days per week, and two months, four hours per day, five days per week) with a mean concentration of 9 ± 0.9 mg/m^3. Signs of toxicity in rats included: an increased number of leukocytes in males; some irritation of the hematopoietic tissue (namely the red portion of the bone marrow); disruption of liver function; and a slight decrease in the activity of the pituitary-adrenal system. In guinea pigs there was an increase in the number of eosinophils. Morphological studies showed symptions of irritation in the upper respiratory tract, and inflammation, edema, and perivascular sclerosis in the lungs in both species. Kurlyandskii, et al. (1975) reported that chronic exposure (time not reported) of rats to 0.5 mg/m^3 mixed cresols decreased the level of gamma-globulin in the serum, increased excitability of the central nervous system, and caused functional changes in the lungs and liver, but no supporting data are available.

e. Dermatological and Sensitization Studies

(1) Human Data

As previously noted, the cresols are strong corrosives. Cutaneous application causes local tissue corrosion, burns, and dermatitis. Certain individuals are hypersensitive to cresols (Deichmann and Keplinger, 1963). There have been numerous cases of burns and skin corrosion from acute contact with cresols in the industrial environment (Anon., 1940; Goodman, 1933; Zalecki, 1965). Herwick and Treweek (1933) reported a case of burning and/or sensitization from dermal contact with cresols in which a patient was exposed for two hours to an anesthesia mask which had been sterilized a week previously in a solution containing approximately 10% of a "compound solution of cresol." When the mask was removed, there was marked erythema of the face. This became worse, with blistering of the skin. Scarring from the burns was still present one year following the accident. The authors determined that the mask could have contained from 21.1 to 64.2 mg of cresols. In another study, p-cresol tested at a 4% concentration in petrolatum produced no sensitization or irritation reactions in 25 volunteers (Kligman, 1966; Kligman, 1972) after a either a "maximization test or a 24-hour closed patch test."

(2) Animal Data

Cresols also have dermatological effects in experimental animals. When p-cresol was applied full strength to intact or abraded rabbit skin irritation was produced (Denine, 1973). When applied to the skin of rats (at the LD_{50} concentrations), the various cresols produced skin necrosis (Uzhdavini and Gilev, 1976). p-Cresol has been identified as the active chemical in a laundry ink which caused depigmentation of hair in mice (Shelley, 1974). The mice in the experiment were treated topically three times a week for six weeks with a 0.5% p-cresol solution in acetone following plucking or clipping of the hair. It has been suggested that the structure of p-cresol may mimic the structure of tyrosine, the amino acid building block for melanin, and, thereby, inhibit the production of melanin. The authors believe it is more likely that tyrosinase acts on p-cresol to form free radical derivatives that may initiate lipid peroxidation with consequent permanent damage to or destruction of melanocytes.

f. Neurotoxicity

Most of the toxic effects produced by the cresols involve central nervous system (see Section C.2.d., Systemic Toxicity). Because of this, these chemicals can be considered neurotoxins.

g. Behavioral Toxicity

No information was found in the literature specifically on the behavioral toxicity of the cresols.

h. Metabolism

(1) Pharmacokinetics and Distribution

The cresol isomers are absorbed through the skin, open wounds, and mucous membranes of the gastrointestinal and respiratory tracts of mammals (Deichmann and Keplinger, 1963). There is only limited data on the rate of absorption, however. In one study, the rate of absorption for p-cresol orally administered to fasting rats, was 3 mg per 100 g body weight per hour during the first 15 minutes. The rate of phenol absorption at the same point was 14 mg per 100 g body weight per hour (Mareque and Marenzi, 1937). Other reports reviewed by Deichmann and Keplinger (1963) indicate that the rate of absorption of cresols is similar to that of phenol, but the data are not available (Embody, *et. al*., 1940; Hunaki, 1940; Klinger and Norton, 1945).

There is little information available on the tissue distribution of the cresols, but *post mortem* examination of humans accidentally poisoned with generic lysol have been reported. Bruce, *et al*. (1976)detected mixed cresols by gas chromatography in two humans poisoned by lysol ingestion as follows:

Material	Case 1	Case 2
Blood (mg per 100 ml)	19·0	7·1
Urine (mg per 100 ml)	30·4	NA
Brain (mg per 100 g)	NA	0·28
Liver (mg per 100 g)	48·0	90·0
Kidney (mg per 100 g)	NA	39·6
Stomach contents (g)	3·2	0·4

Source: Bruce, *et al*., 1976

The major route of excretion for the cresols is in the urine, but some has been reported to be excreted in the bile (Wandel, 1907). The rate of excretion in rabbits has been described by Bray, *et al*. (1950).

The 24-hour urinary excretion products were reported as follows:

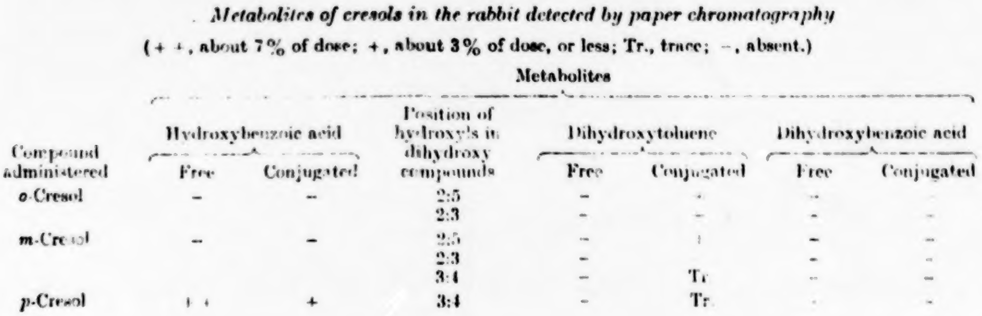
Compound administered	Excretion products: Type	Percentage of dose excreted: Range	Percentage of dose excreted: Average
o-Cresol (500 mg.)	Ethereal sulphate	13-19	15
	Ether glucuronide	55-91	72
	Free cresol	0-2	1
	Total cresol	75-83	80
m-Cresol (500 mg.)	Ethereal sulphate	4-15	10
	Ether glucuronide	53-70	60
	Free cresol	0-4	1
	Total cresol	81-86	84
p-Cresol (250-500 mg.)	Ethereal sulphate	12-21	15
	Ether glucuronide	32-85	61
	Free cresol	0-12	2
	Total cresol	52-85	65

Source: Bray, et al., 1950

(2) Metabolic Modification

Evidence from experimental animals indicates that the cresols are oxidized and/or conjugated with either sulfuric or glucuronic acid in vivo. In early experiments Bauman and Herter (1877; 1878) observed that commercial cresols (probably a mixture) administered orally, resulted in the formation of urinary sulfate in the horse and dog. Neuberg and Kretschmer (1911) demonstrated conjugation of the hydroxyl group in p-cresol with glucuronic acid by isolation of the metabolite from the urine of dogs treated with p-cresol. Jonescu (1906) showed that sulfuric and glucuronic acid conjugates of cresols were excreted in the urine of dogs; in an unspecified amount of time, 30-50% of the administered o-cresol, 46.5-50% of the m-cresol, and 23-27% of the administered p-cresol were excreted as conjugates. As early as 1881, Preusse found that the dog oxidized p-cresol to p-hydroxybenzoic acid and o-cresol to 2,5-dihydroxytoluene.

Rabbits metabolize the cresols in the same manner as dogs. Deichmann and Thomas (1943) noted that orally administered o-, m-, or p-cresol caused a marked rise in urinary glucuronic and sulfuric acids in rabbits one to four days after treatment. Williams (1938) found that the percentages of doses of the various isomers excreted in the rabbit urine as the sulfate conjugate were 22% (for o-cresol and m-cresol) and 16% (for p-cresol). The experiments of Bray, et al. (1950) elucidated the metabolism of the cresols in rabbits. Using paper chromatography, they determined the urinary metabolites following single oral doses of 500-600 mg o- or m-cresol, or 200-300 mg p-cresol. The following table summarizes their findings from 24-hour rabbit urine:



Metabolites of cresols in the rabbit detected by paper chromatography

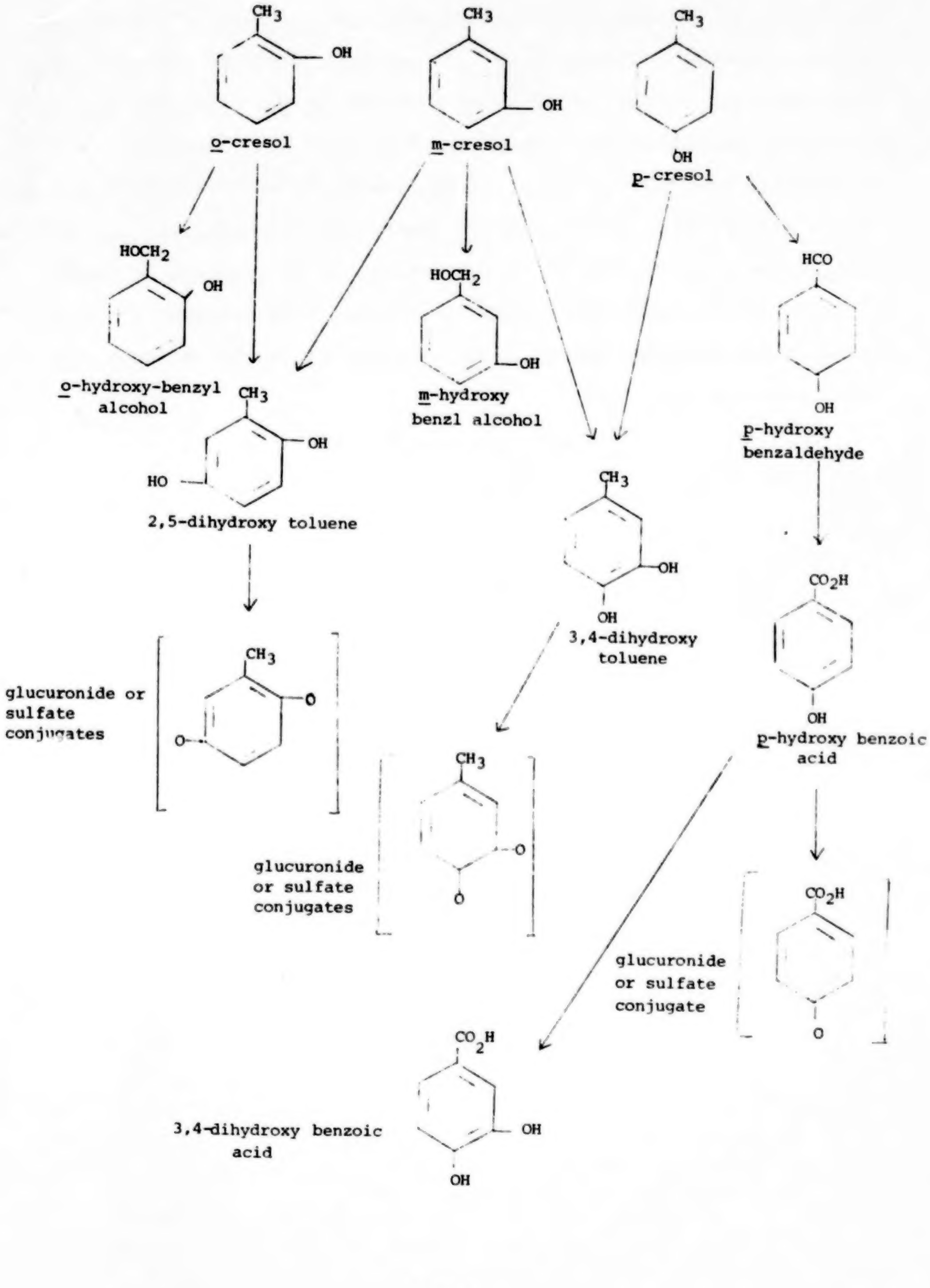
(+ +, about 7% of dose; +, about 3% of dose, or less; Tr., trace; –, absent.)

Compound administered	Metabolites: Hydroxybenzoic acid		Position of hydroxyls in dihydroxy compounds	Dihydroxytoluene		Dihydroxybenzoic acid	
	Free	Conjugated		Free	Conjugated	Free	Conjugated
o-Cresol	–	–	2:5	–	+	–	–
			2:3	–	–	–	–
m-Cresol	–	–	2:5	–	+	–	–
			2:3	–		–	–
			3:4	–	Tr	–	–
p-Cresol	+ +	+	3:4	–	Tr	–	–

Source: Bray, et al., 1950

Studies in vitro with rat liver suggest similar metabolic transformation for p- and o-cresol (Sato, et al., 1956). p-Cresol was converted sequentially to p-hydroxybenzyl alcohol, p-hydroxybenzaldehyde, p-hydroxybenzoic acid, and 3,4-dihydroxybenzoic acid. o-Cresol was converted to 2,5-dihydroxy toluene and a trace of o-hydroxy benzyl alcohol; m-cresol was converted to 2,5-dihydroxy toluene and m-hydroxy benzyl alcohol.

From these studies in vivo and in vitro, the following metabolic modification sequence can be constructed.


CH3
OH
o-cresol
CH3
OH
m-cresol
CH3
OH
p-cresol
HOCH2
OH
o-hydroxy-benzyl alcohol
HOCH2
OH
m-hydroxy benzl alcohol
HCO
OH
p-hydroxy benzaldehyde
CH3
OH
HO
2,5-dihydroxy toluene
CH3
OH
OH
3,4-dihydroxy toluene
CO2H
OH
p-hydroxy benzoic acid
glucuronide or sulfate conjugates
CH3
O
O
glucuronide or sulfate conjugates
CH3
O
O
glucuronide or sulfate conjugate
CO2H
O
CO2H
OH
OH
3,4-dihydroxy benzoic acid

No information was found on the metabolism of cresols in humans, but it should be noted that free cresols, particularly p-cresol, are normally present in human urine. It has been reported that the normal human excretes from 16 to 39 mg of p-cresol in the urine per day (Deichmann and Keplinger, 1963). From studies with germ free rats, it is apparent that this p-cresol is the result of metabolic action of the normal gastrointestinal microflora (Bakke and Midtvedt, 1970). Studies *in vitro* have shown that it is the metabolism of tyrosine by these bacteria in the human gastrointestinal tract that produces the p-cresol which is subsequently absorbed and excreted in the urine (Bone and Tamm, 1976; Bone, *et al*., 1976).

IV. References for Alkyl Phthalates

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APPENDIX A

Aquatic Toxicity Rating

Chemicals are rated on the basis of their toxicity to aquatic life. Finfish were selected as one of the most sensitive groups for which toxicological data are available with information on shrimp and other aquatic organisms being used to fill in the gaps. The 96 hour TL_m test* was used to provide the basis for making five rankings of the toxic potential. It was considered that if the substance would not be lethal according to this test at greater than 1,000 mg/l then it posed no major toxic hazard to aquatic life.

The system rankings are outlined below.

Grade	Description	TL_m Concentration
0	Insignificant hazard	>1,000 mg/l
1	Practically non-toxic	100-1,000 mg/l
2	Slightly toxic	10-100 mg/l
3	Moderately toxic	1-10 mg/l
4	Highly toxic	<1 mg/l

Most of the 96 hour TL_m test data available were derived from tests with adult or juvenile aquatic organisms, usually from upper levels of the food chain. It was recognized, however, that other stages, e.g., larvae or eggs, or organisms lower but critically important in the food web, might be much more susceptible than the organisms or the stages of organisms that were tested.

Although it was believed that at the present time acute toxicity TL_m data are more complete and, therefore, present the best method of ranking substances according to hazard, it was recognized that chronic or sub-lethal effects may ultimately be more important ecological considerations. Fish are known to be able to detect concentrations as low as 10^{-3} to 10^{-8} mg/l of a range of substances. Behavior and chemo-reception (as involved in food finding, mating, migration) might be adversely affected by concentrations considerably lower than the 96 hour TL_m.

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*TL_m-- The concentration of a substance which will, within a specified period of time (generally 96 hours) kill 50% of the exposed test organisms. The concentration is usually expressed in parts per million (mg/l). The bioassay may be conducted under static or continuous flow conditions.

For many of the chemicals no published aquatic toxicity data are available. In these cases, the ratings were estimated from physical properties and by extrapolation of data from chemically similar compounds. Some of the estimates used those of the previous rating list, adjusted for the revised toxicity scales. Ratings for substances for which no toxicity data have been located are given in parenthesis. Where information was available for more than one of the preferred aquatic organisms, the figure for the most susceptible species was generally used.

Rating Reductions

Consistent with the rating of other pollution hazards, these ratings were modified in some cases for chemicals having low water solubility or high volatility, which accordingly, will not normally pollute waters. A TL_m concentration value was taken as prima facie evidence that a lethal concentration in water can be reached. Adjustments to aquatic toxicity ratings based on low water solubility are made only where it can be shown that reported TL_m concentrations were acheived in the laboratory by techniques that would not be available in normal situations.

Similarly, highly volatile substances which are insoluble and tend to float on the surface are reduced in ratings. Where any doubt existed, the ratings were not reduced. The rationale for a reduction is given in the discussion section of the ratings.